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CONTENTS

PAGE

Nodule Formation in Rheumatic Disease. G. D. KERSLEY, H. J. GIBSON AND M. H. L. DESMARAIS 141

Pleuropneumonia-like Organisms and Arthritis. G. M. FINDLAY 153

The Nature of Fibrositis. III. Multiple Lesions and the Neural Hypothesis. MICHAEL KELLY . 161

The Incidence of Rheumatism. BRYCE R. NISBET 168

Review of Gout, 1939–1946. L. C. HILL 171

Heberden Society, Annual General Meeting 177

Fellowship of Postgraduate Medicine 179

Obituaries 180

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NODULE FORMATION IN RHEUMATIC DISEASE

BY

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and

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The literature on nodule formation in rheumatic disease is confused by the absence of co-ordination of clinical data and pathological material. Nodules of one sort or another are found in many rheumatic syndromes, and also in conditions which are barely within the scope of that designation. Parkes Weber (1943) classified nodules into eight types: those occurring in acute rheumatism, rheumatoid arthritis, gout, xanthomata, calcinosis, amyloidosis, mucinous (in thyroid dysfunction), and those occurring in the Ehlers-Danlos syndrome of laxity, abnormal elasticity, atrophy, and friability of the skin and ligaments. While the types of nodule found in acute rheumatism and rheumatoid arthritis are becoming fairly well defined (Dawson, 1933; Collins, 1939; and Bennett, 1943), there is still much debate on their structure in fibrositis, Copeman and Ackerman (1944) believing them to be fatty herniations, and Elliott (1944) supporting the view that they are only areas of spasm of muscle fibres.

It was, therefore, decided to keep separately careful clinical records and biopsy reports on all cases of rheumatic or pseudo-rheumatic disease where nodules were definitely palpable, and later to classify them clinically, comparing their clinical diagnoses with the findings of the pathologist. Twenty-seven cases have been so examined.

CASE 1

A farmer, aged 24, gave a history of typical tophaceous gout of five years' duration, with frequent acute attacks and periods of complete remission. Tophi were present in both ears, elbows, and hands, and in the right knee. Radiographs showed the typical appearances of gout, with "punched-out" areas but no generalized osteoporosis or loss of joint space. Over a period of three years the blood uric acid varied between 3·8 mg. and 8 mg. per 100 c.cm. of blood. The haematocrit reading was persistently normal or above normal, and the corrected suspension stability test (C.S.S.) fluctuated between 54% and 66%. A nodule on the right elbow was excised for section. As he was an adopted child no family history was available.

Macroscopically, the tissue excised consisted of a fibrous wall surrounding a loculated cavity filled with a paste of biurate crystals.

Microscopic Findings (Fig. 1).—Underlying the true skin, fibrous tissue strands were present forming loculi of varying size and rounded shape, and containing hyaline amorphous material impregnated with acicular crystals of biurate. The walls of these spaces showed a proliferation of young fibroblasts, often with a radial alignment similar to those seen round necrotic areas in the nodule of rheumatoid arthritis. Also present were many foreign-body giant cells of small size, containing up to six nuclei. The appearances were those of a subcutaneous gouty tophus.

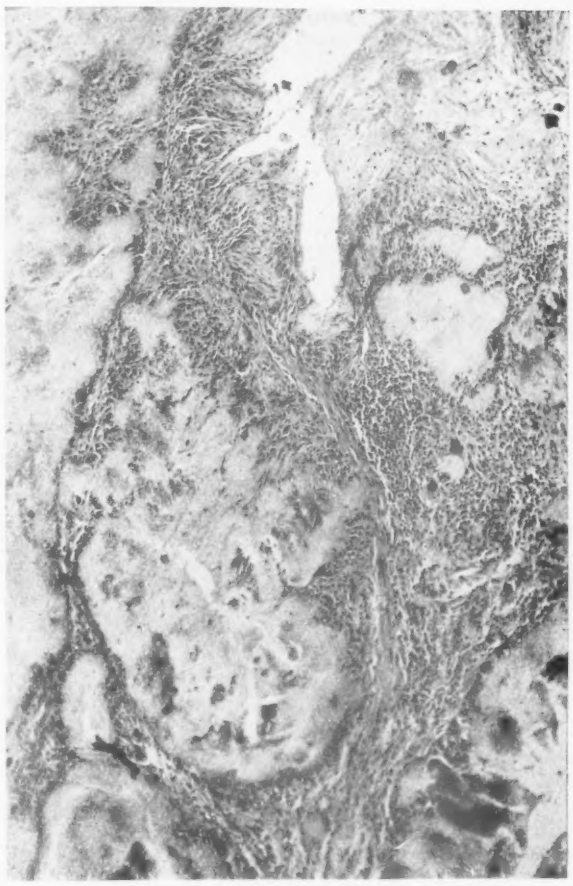

FIG. 1.—A subcutaneous nodule from a typical case of gout (Case 1). It consists of fibrous septa enclosing areas of hyaline amorphous material in which biurate crystals are present. Along the septa there is a marked fibroblastic reaction. Giant cells of foreign-body type and lymphocytes are also seen. Haematoxylin and eosin. × 100.

CASE 2

A man, aged 68, with no family history of gout, first noticed swelling of the proximal interphalangeal joint of his left index finger fifteen years ago. The swelling had gradually increased in size to that of a tangerine, and the other fingers became similarly affected. Two years later the condition spread to the toes, and then to the olecranon bursae of the elbows and the right knee. There were no acute attacks or remissions, and there was but little pain, but gradually tophaceous material became apparent. Six years ago one of the toes was so deformed and swollen that it had to be amputated, and for the same reason a finger was removed four years ago. About this time one of the olecranon bursae burst, tophaceous material bespattering the wall when the elbow was flexed. The patient was, apart from the joint condition, physically fit and had slowly gained in weight. The blood uric acid seven years ago was 6 mg. per 100 c.cm. of blood, and the plasma uric acid is now 9·0 mg. per 100 c.cm. The blood cholesterol was 150 mg. per 100 c.cm. The nodule was a typical subcutaneous gouty tophus. The dermis showed dense round-cell accumulations in close relation to the vessels. Lymphocytes were the predominant cell. The main mass of the nodule consisted of areas of hyaline degeneration heavily infiltrated with biurate crystals and outlined by fibrous septa containing fibroblasts, mesenchymal cells, and many giant cells.

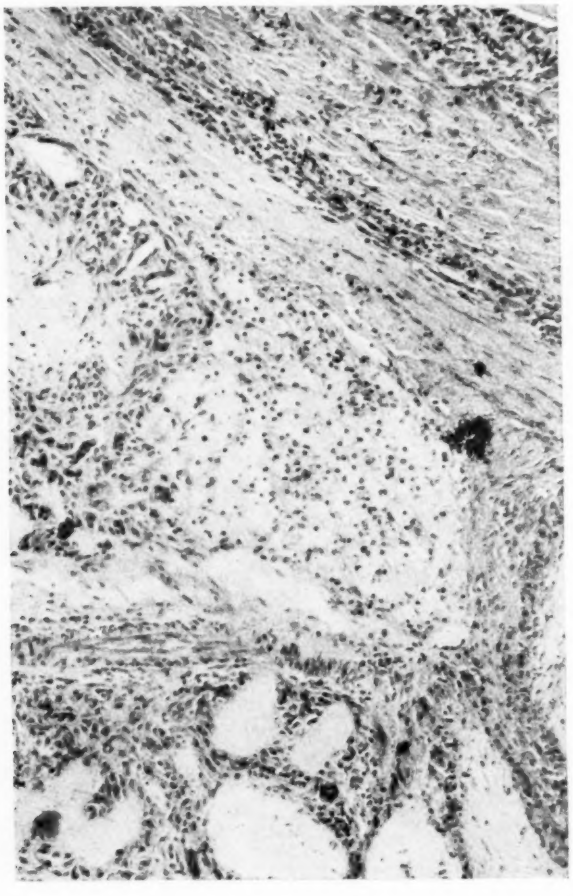

FIG. 2.—Subcutaneous nodule from toe of a typical case of advanced gout (Case 2). Among the usual cellular features shown in Fig. 1, was found an island of large polyhedral cells with small, round, darkly stained nuclei and vacuolated cytoplasm. They resemble morphologically the "foam cells" seen in Case 14. Haematoxylin and eosin. × 100.

In one area, in the space where three rounded necrotic areas met, was seen a group of large polygonal cells with small round nuclei towards the centre (Fig. 2). The nuclei contained a varying amount of chromatin and an eccentric nucleolus. The cytoplasm was granular and vacuolated, and the thin nuclear membrane clearly defined. These cells closely resembled the "foam cells" described by Fletcher (1946). They have not been found in other gouty material.

CASE 3

A docker, aged 55, gave a history of rheumatoid arthritis of three years' duration. The joints were symmetrically involved, with a mild degree of fusiform swelling of the fingers and slight muscle wasting of the forearms and interossei. There had been no marked loss of weight. The condition on admission was fairly active, as shown by the decreased C.S.S. (56%), the low haematocrit (38%) and acute pains in the knees, feet, and hands. Radiographs of the hands were typical of rheumatoid arthritis. A nodule of two years' duration on the left elbow was excised for examination. The section showed a large nodule 20 mm. × 18 mm. lying in and deep to the cutis. The skin was normal. At the level of the deeper sweat glands the nodule proper commenced. It consisted of fibrous tissue in which were numerous areas of necrosis surrounded by a palisade layer of radially arranged mesenchyme cells of fibroblastic type. The necrotic foci showed an inner zone of complete necrosis of slightly basophil tint, and in some cases this showed fissures and commencing cavitation. Surrounding the area of complete necrosis there was a zone, adjacent to the palisade layer, in which destruction of the collagen fibres was incomplete and which showed the reticulated structure of fibrinoid degeneration. Within all the necrotic zones, which appeared to be continuous with one another by narrow bands of necrosis, nuclear fragments were present. At the periphery of the nodule fibrous tissue was seen with broad collagen bundles and numerous vessels. Many of the latter showed thickened walls; and, where a necrotic area was in close proximity, complete obliteration of the lumen had occurred. The appearances were typical of the rheumatoid arthritis nodule as described by Dawson (1933) and Collins (1937).

CASE 4

A man, aged 42, gave a history of typical rheumatoid arthritis of thirteen years' duration, and a recent flare-up. The condition was fairly active as shown by the C.S.S. (63%). There was no secondary anaemia, but he had lost some weight before admission. The radiographs were typical of rheumatoid arthritis with early secondary osteo-arthritic changes. He had had two courses of gold therapy with fairly good response. A nodule about the size of a walnut, which had first appeared six years before on the right elbow, was excised under a local anaesthetic and was found to be typical of rheumatoid arthritis, as described in Case 3. Very extensive necrosis was present, with widespread early disintegration and commencing liquefaction of the necrotic tissue to form small cystic cavities. The extent of necrosis due to coalescence of separate foci is consistent with the six years' duration of this nodule.

CASE 5

A man, aged 64, gave a history of rheumatoid arthritis of ten years' duration. On admission the condition was active, with a lowered C.S.S. of 65%, and loss of weight. The blood uric acid was normal, and the Berger Test

negative. Repeated examinations of the sputum showed no tubercle bacilli. Radiographs showed the appearance of advanced rheumatoid arthritis. There were multiple nodules on the elbows, sacrum, and scalp. A nodule on the left elbow was excised.

On section the nodule showed an inner zone of very dense fibrous tissue with few nuclei and an appearance of scar tissue. In this were a few elongated masses of eosinophil fibrinoid material with a surrounding zone of radially arranged fibroblasts and larger primitive mesodermal cells as seen in rheumatoid nodules. The peripheral zone was vascular and the vessels were associated with a copious lymphocytic infiltration. The lymphocytes were para-vascular in their distribution, and the appearances resembled closely those found in nerve and muscle in rheumatoid arthritis. Thus the nodule, while definitely of rheumatoid type, presented unusual features—a condensation of fibrous tissue, and abundant round-cell reaction around vessels in the peripheral zone.

CASE 6

A commercial traveller, aged 40, gave a history of rheumatoid arthritis of three years' duration. The right ankle was the first joint to be involved, but within three years the knees, elbows, and hands were affected. The C.S.S. was 61%; the haematocrit 40%, and the blood uric acid 3·4 mg. per 100 c. cm. of blood. Radiographs of the hands showed changes of rheumatoid type with translucent areas simulating gout. From the onset the patient developed nodules on the middle finger of the left hand. Within a year they were present on the knees and elbows, and a nodule on the right elbow was excised for section. The histology was typical of rheumatoid arthritis without any unusual features.

CASE 7

A man, aged 49, gave a history of rheumatoid arthritis of five years' duration. The C.S.S. was 63%, the haematocrit 45%, and blood uric acid 1·8 mg. per 100 c.cm. of blood. A subcutaneous nodule was excised from the elbow under local anaesthetic. The nodule was typical of rheumatoid arthritis, as previously described.

CASE 8

A housewife, aged 41, had had clinical signs of atypical rheumatoid arthritis for five years. She gave a history of generalized pains in all her joints except the hips and knees, the onset following soon after an air raid. The disease was still active at the time of examination, with progressive loss of weight and a decreased C.S.S. (67%). There was no anaemia and the plasma uric acid was normal, 5·1 mg. per 100 c.cm. of blood. Radiographs of the hands showed changes of gouty type with well marked "punched out" areas. There was, however, no family history of gout. Subcutaneous nodules of the size of walnuts appeared on the elbows two years before admission, and one of these was excised for microscopic examination. The tissue showed the characteristic structure of a rheumatoid arthritic nodule. It was an early example, showing numerous proliferative foci, fibrinoid and necrotic lesions, with the usual radial fibroblastic reaction. There was no suggestion of gout.

CASE 9

A park-keeper, aged 56, appeared clinically to have had acute rheumatoid arthritis for three years. Throughout the illness the haematocrit had, however, been normal, the C.S.S. fluctuated between 59% and 79% and the blood uric acid between 2·5 mg. and 4·2 mg. per 100 c.cm. of blood. There was no history of gout or rheumatism in the family. Two years after the onset a subcutaneous nodule appeared in the right elbow, and since then multiple subcutaneous nodules had appeared over the ulnar surface of both forearms, the scapulae, iliac crests, and patellae, varying in size from a small pea to a walnut. A nodule was excised from the right elbow for section and examination. The section showed the characteristic structure of a rheumatoid arthritic nodule, with extensive areas of necrosis. Giant cells were numerous in some fields at the margin of the necrotic zones.

CASE 10

A transport driver, aged 39, gave a history of sudden onset of pain and swelling of hands and fingers four years previously. At about the same time painful subcutaneous nodules appeared on the elbows. These had gradually grown bigger, and at the time of excision had reached the size of large cherries. A year previously he had developed thyrotoxicosis with loss of weight and further involvement of the left shoulder, ankles, and jaws. A partial thyroidectomy was performed, and since then the patient's condition had improved. On admission there was no secondary anaemia, the C.S.S. was slightly raised (73%) and the plasma uric acid was 4·7 mg. per 100 c.cm. Radiographs of the hands showed changes of rheumatoid arthritic type. The section was taken from a nodule from the right elbow and showed a typical rheumatoid arthritis structure. In the true skin lymphocytic foci were seen round and near small arteries. Arteritis was present in many of the smaller vessels.

CASE 11

A retired Army pensioner, aged 56, gave a history of arthritis of the rheumatoid type of fourteen years' duration. The knees, elbows, and wrists were the joints mostly affected. There was flexion, deformity and marked limitation of movement. The C.S.S. was normal (86%), there was no anaemia (haematocrit 50%), and the blood uric acid was 4·2 mg. per 100 c.cm. of blood. A small nodule had been present on the right elbow for four years and was recently getting smaller. This was excised for section. It consisted of fibrous tissue and fat. There was some slight leucocytic infiltration and a few areas of hyaline degeneration, but no fibrinoid change, necrosis, or evidence of characteristic rheumatoid reaction. Patches of haemorrhage were present, and a cleft ran through the middle of the nodule, lined in part by a flattened layer of fibrous tissue. The histology was that of a traumatic nodule commencing to form an adventitious bursa.

CASE 12

A printer's foreman, aged 51, gave a history of gradual onset of pain and stiffness in the right elbow and left knee twelve years before admission. He continued with his work for another two years, when he noticed tha "his memory was deteriorating and that he could not grasp things quickly"; his speech became slurred and his voice husky. His hair and the outer halves of his eyebrows were rapidly thinning out, and over a period of four months he had put on three stone in weight. He was diagnosed as suffering from myxoedema, and thyroid was administered, with great improvement in all his symptoms. Nine years ago he developed pain and swelling of his hands and fingers and feet; he gradually developed all the signs and symptoms of rheumatoid arthritis, with a C.S.S. of 64%, fusiform swelling of

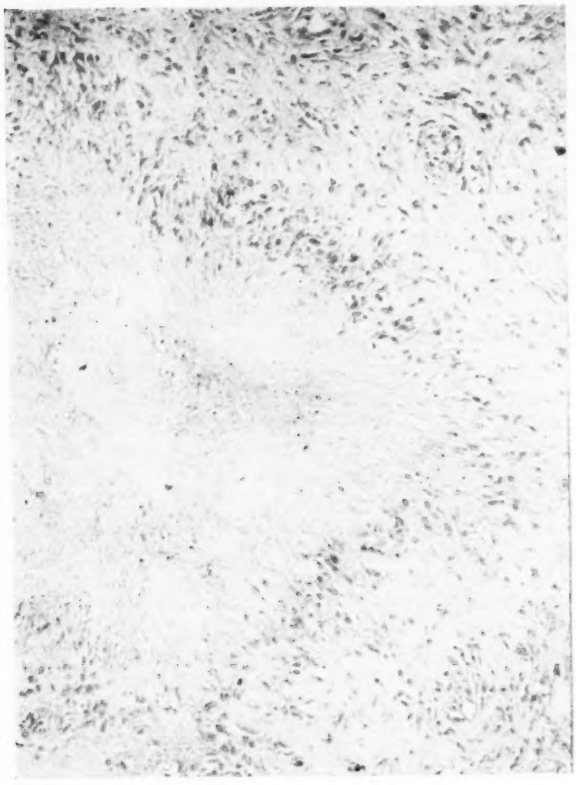

FIG. 3.—A subcutaneous nodule from Case 12. This illustrates the typical rheumatoid focus consisting of central necrotic zone surrounded by a palisade layer of radially arranged mesenchymal cells, within a fibrous mass. Haematoxylin and eosin. × 100.

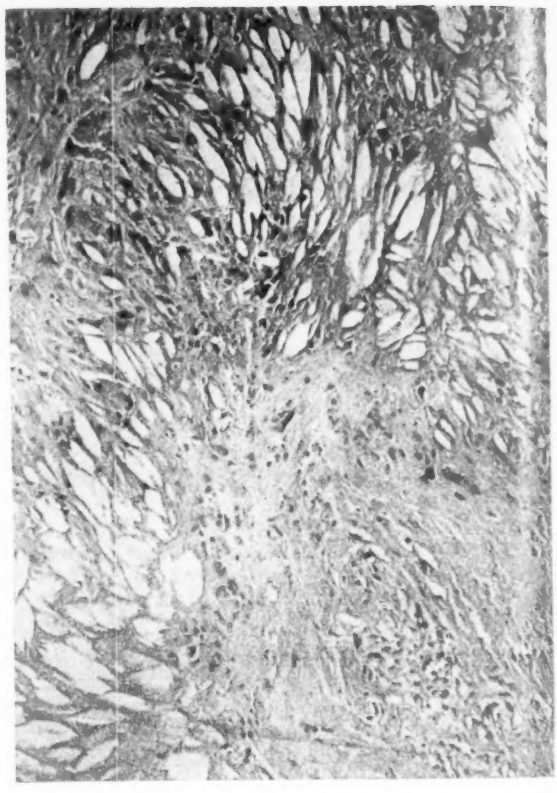

FIG. 4.—Another part of the same nodule as seen in Fig. 3 (Case 12). Extensive cholesterol infiltration is present, with a giant cell reaction. In preparing the section the cholesterol has been dissolved, leaving large fusiform clefts in the tissues. Cholesterol crystals were demonstrated in the fresh material. Haematoxylin and eosin. × 100.

fingers, and flexion deformity of elbows and knees. The blood uric acid was 4·2 mg. per 100 c.cm. of blood; the haematocrit 40%, the blood cholesterol was raised to 287 mg. per 100 c.cm. and his basal metabolic rate was 36. At the time of admission his general condition had improved slightly, and he was keeping a constant weight on a grain of thyroid daily. The blood cholesterol was normal (143 mg. per 100 c.cm.) the C.S.S. was 58%, the haematocrit 35%, and the Berger test negative. Radiographs of the hands showed typical changes of rheumatoid arthritis. A nodule which had been present on the right elbow for eight years was excised under a local anaesthetic.

The nodule was 23 mm. × 18 mm. and macroscopically it showed a number of yellow areas 2 to 3 mm. in diameter scattered towards one end, while the structure elsewhere was of usual fibrous nature. Microscopically (Figs. 3 and 4) a typical rheumatoid nodule structure with many small necrotic foci and radially arranged fibroblasts was seen in one part of the tissue. Elsewhere the structure was quite different. The palisade layer was much less definite, the cells being smaller and less regularly arranged. The central necrotic zone was heavily infiltrated by cholesterol. In stained sections this was seen as a loose meshwork of clefts with narrow bridges of amorphous hyaline material separating them. The yellow zones in the fresh material, when scraped, yielded abundant cholesterol crystals. Adjacent to the areas of lipoid infiltration there were giant cells of foreign-body type. These showed abundant cytoplasm and appeared in some cases to be attempting to engulf the adjacent cholesterol. In that part of the nodules where the cholesterol was situated the surrounding fibrous tissue was more hyaline and less cellular than elsewhere. No " foam cells " were seen, but the nodule in this case appeared to have much in common with those described by Fletcher (1946), in that there was an association of lipoid deposition with an atypical rheumatoid histology in some parts, while elsewhere the picture was typical of rheumatoid arthritis.

CASE 13

A boiler hand, aged 53, gave a history of increasing pain and stiffness of the knees, hands, and fingers for four years. He had been very much overweight (19 stone), with a myxoedematous appearance, bilateral genu valgum, and abnormal deposition of fat round the hips and thighs. He reacted well to thyroid, gr. 2 daily, by steady loss of weight and increased feeling of well-being. The C.S.S. was decreased (62%), but there was no anaemia, and the plasma uric acid was 5·0 mg. per 100 c.cm. Radiographs of the knees showed changes of osteo-arthritic type. Multiple nodules had appeared along the ulnar borders of the forearms eighteen months before admission, and a nodule was excised from the left elbow for microscopic examination. The section (Fig. 5A, B) showed (1) rheumatoid arthritic necrotic foci in one small area; (2) two cholesterol foci of unusual appearance, oval, with concentric layers of hyaline eosinophilic fibrous tissue with commencing cavitation and cholesterol deposits in the centre; (3) throughout the true skin, subcutaneous fat and fibrous tissue there

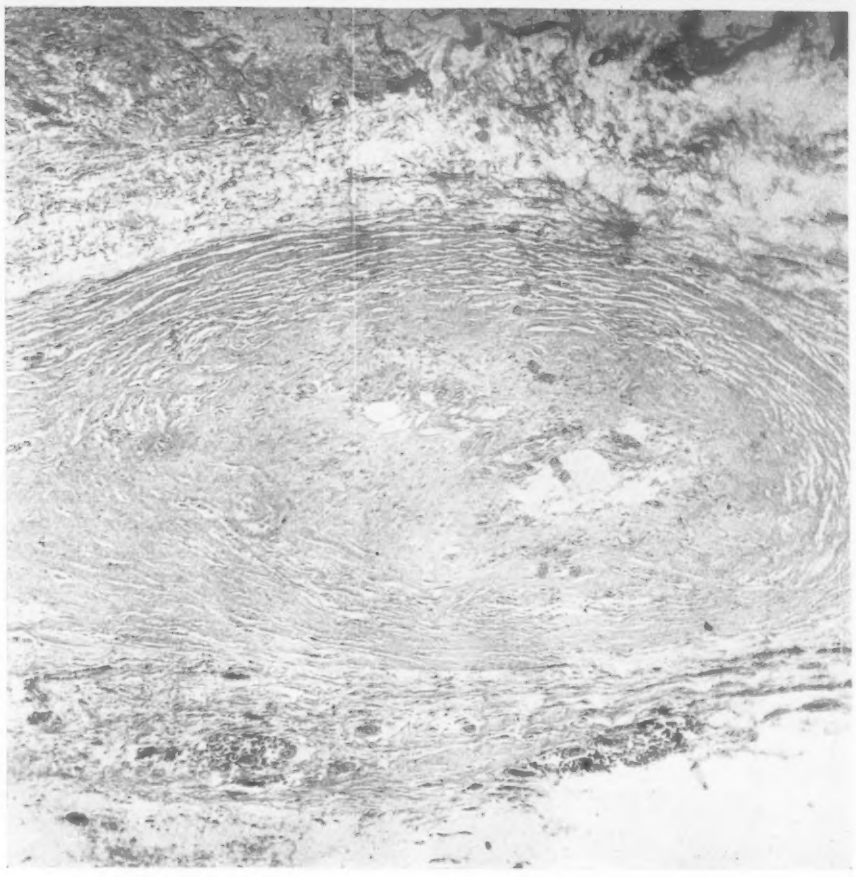

FIG. 5A.—Subcutaneous nodule from Case 13, showing an oval mass of dense hyaline fibrous tissue, in the centre of which are cholesterol clefts. No palisade layer of mesenchymal cells is present. Haematoxylin and eosin. × 100.

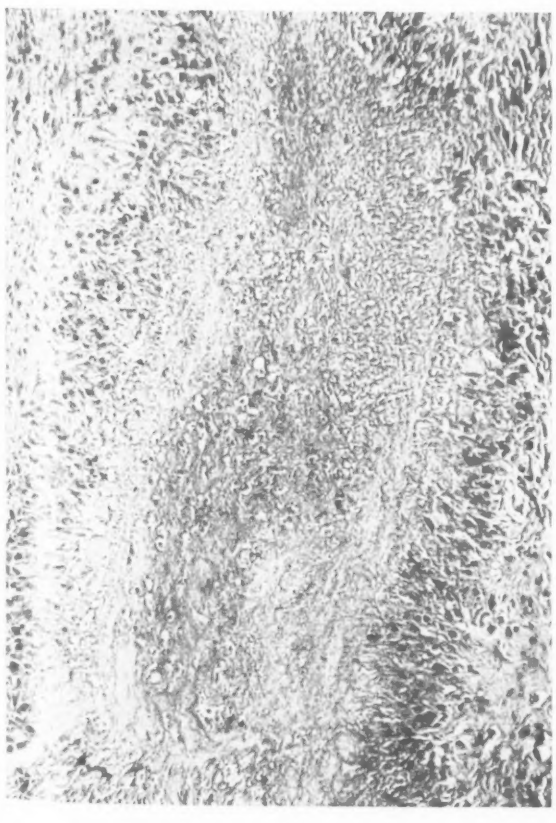

FIG. 5B.—Another field from the same specimen as 5A, showing typical rheumatoid structure. Haematoxylin and eosin. × 100.

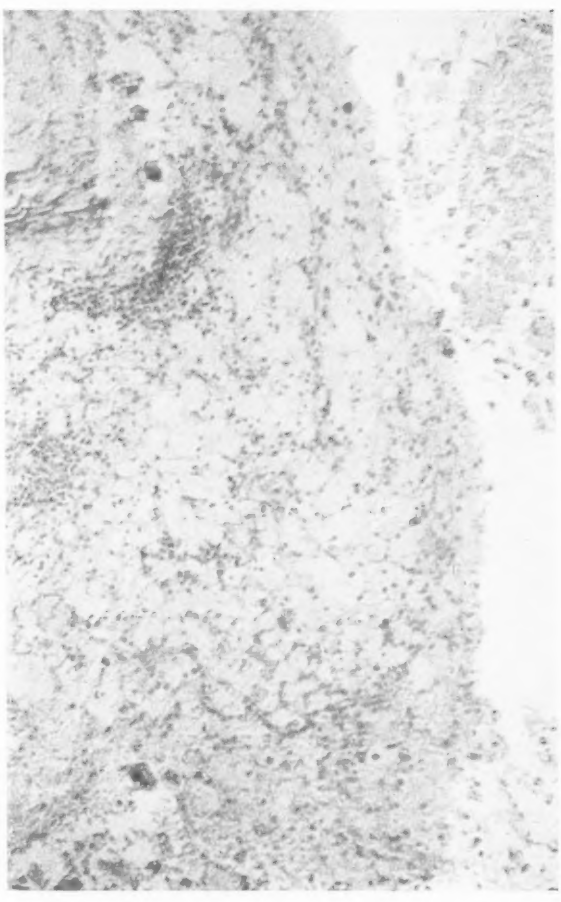

FIG. 6.—Mass from shoulder region of a fatal case of rheumatoid arthritis (Case 14). It consists mainly of necrotic tissue containing lipoid, but patches of large vacuolated "foam cells" are also seen. Haematoxylin and eosin. × 100.

were large peri- and para-vascular cell accumulations consisting of lymphocytes, plasma cells, and some polymorphs, comparable in extent with the Allison and Ghormley nodes of synovial membrane.

CASE 14

A male civil servant, aged 48, who had suffered from severe rheumatoid arthritis for nine years, was described in our previous paper on muscle changes in rheumatoid arthritis (Gibson, Kersley, and Desmarais, 1946; Case 10).

Necropsy.—At necropsy he was found to have a broken-down nodular mass in the region of the right shoulder, which on section showed "foam cells" containing cholesterol (Fig. 6). Some fields bore a striking resemblance to some of those seen in a nodule from the advanced case of gout (Case 2, Fig. 2). Adjacent to the shoulder joint there was a sausage-shaped mass which consisted of a fibrous capsule enclosing a soft yellow greasy necrotic material. Sections showed, in addition to granular amorphous debris: (1) cholesterol clefts in hyaline fibrous tissue; (2) areas of large rounded or polygonal cells with small, darkly stained nuclei and well-defined cell membrane; the cytoplasm was vacuolated; they resembled closely the "foam cells" described by Fletcher (1946) in a rheumatoid nodule, and also those seen in the nodule from Case 2.

CASE 15

A chairmaker, aged 52, had received a pension from 1918 to 1920 for "rheumatism" in the left shoulder. Two years before the biopsy was performed, there had been a gradual onset of pain in the left shoulder, both elbows, both hands, and wrists. The pain was never severe, and there was no history of acute episodes, though he had had pain and swelling in the big toe after walking. On admission he showed an atypical picture of rheumatoid arthritis. The C.S.S. was 72%, the haematocrit 47%, and blood uric acid 2·3 mg. per 100 c.cm. Radiographs of the hands showed changes of the rheumatoid arthritic type, with features suggestive of gout. There was, however, no history of gout in the family. A subcutaneous nodule was excised from the right elbow for section and examination. It showed the characteristic appearances of a rheumatoid arthritic subcutaneous nodule. Numerous areas of necrosis were present with radially arranged mesenchymal cells surrounding them. The necrotic foci had coalesced, producing very large areas in which liquefaction had occurred with cavity formation.

CASE 16

A collier, aged 49, gave a history of twenty-one years of acute attacks of joint pains and swelling with periods of complete remission between the attacks. There had never been any appreciable loss of weight. The last attack was a month before admission, when the hands, elbows, and knees had been affected. The C.S.S. was slightly decreased (74%) but the haematocrit was normal (44%). The plasma uric acid was 4·2 mg. per 100 c.cm., and the blood cholesterol of 190 mg. per 100 c.cm. was also normal. Radiographs of the hands showed "punched out" areas suggestive of gout, but clinically the hands were of the rheumatoid type. There was nothing relevant in the family or past history. At the time of the last attack a small subcutaneous nodule the size of a pea appeared in the left elbow. This was excised, and examined and showed the characteristic changes of a rheumatoid arthritic nodule. The nodule was a very early example. Over much of the section the changes were those of fibroblastic proliferation with small patches of fibrinoid change among the young fibroblasts. In two zones, however, necrosis had occurred and the appearances were typical.

CASE 17

A traveller, aged 56, who had for many years been rather depressed, introspective, and dyspeptic, gave a history that after the shock of a "blitz", three years ago, he began to have pain in his feet, spreading to the hands and elbows. Shortly afterwards nodules started to appear, first on the right and then the left elbow, over the interphalangeal joints, on the right patella, left tendo achillis, and over the left eyelid. When once they appeared they grew to sizes varying from that of a pea to a walnut and then remained stationary. Neither pain nor tenderness were features of the nodules. There was little swelling of the joints, but ulnar deviation of the fingers gradually became apparent (Fig. 7). Exacerbations were noticed to be associated with worry. There was some tenderness in certain muscle groups and the intensity of this varied greatly, an area being extremely painful and even showing some swelling for a few days at a time. There was a little restriction of movement of the shoulders, but otherwise mobility was nearly normal. No septic focus was discovered, and, though dyspepsia was a marked feature, radiographs of the gall bladder and stomach were normal. There was little change in weight. The C.S.S. had decreased from 71% to 59% and the haematocrit from 46% to 42%. The blood uric acid increased from 4·2 mg. to 5·0 mg. per 100 c.cm. Radiographs of the hands showed "punched out" areas very similar to those seen in gout (Fig. 8), but there was little, if any, clinical improvement on giving colchicum in full doses. A nodule was excised from the left elbow and was found to be typical of rheumatoid arthritis (Fig. 9). The patient was then given a short course of aurotherapy without benefit, and he has recently had some deep *x*-ray therapy for his hands, with apparently some improvement, no new nodules having appeared and some seeming to be a little smaller.

CASE 18

An Army officer, aged 25, gave a ten months' history of acute rheumatic fever with rheumatic carditis, following on repeated attacks of sore throat. At the same time multiple nodules appeared on the dorsum of the hands, feet, knees, elbows, and the back of the head. Three months later, when the sedimentation rate was normal and his general condition was improving, a fresh crop of nodules appeared and there was some suspicion of fusiform swelling of the fingers with muscle wasting of the interossei of the hands. Radiographs of the hands eight months after the onset of symptoms showed obvious osteoporosis, and a month later the nodules were still present though the sedimentation rate and haematocrit were still normal. His general condition was steadily deteriorating, and examination of the heart showed both aortic and mitral valvular defects. He had lost a quarter of a stone in weight, and the epitrochlear glands were palpable but the spleen was not felt. He was not improved by full doses of salicylates.

A nodule from the left elbow was excised (Fig. 10). It showed a very cellular structure. Young fibroblasts and undifferentiated connective-tissue cells were found in large numbers, with collagen fibres which were undergoing patchy fibrinoid change in many areas. These were conspicuous as bright red-staining zones in the section stained by Masson's method. Some connective-tissue cells were often large, with one, or in certain cases

FIG. 7.—Hands of Case 17. There were many features of gout, but examination of a nodule showed the typical appearance of rheumatoid arthritis.

FIG. 8.—Radiograph of the hands of Case 17, showing changes, including "punched out" areas, similar to those frequently seen in gout.

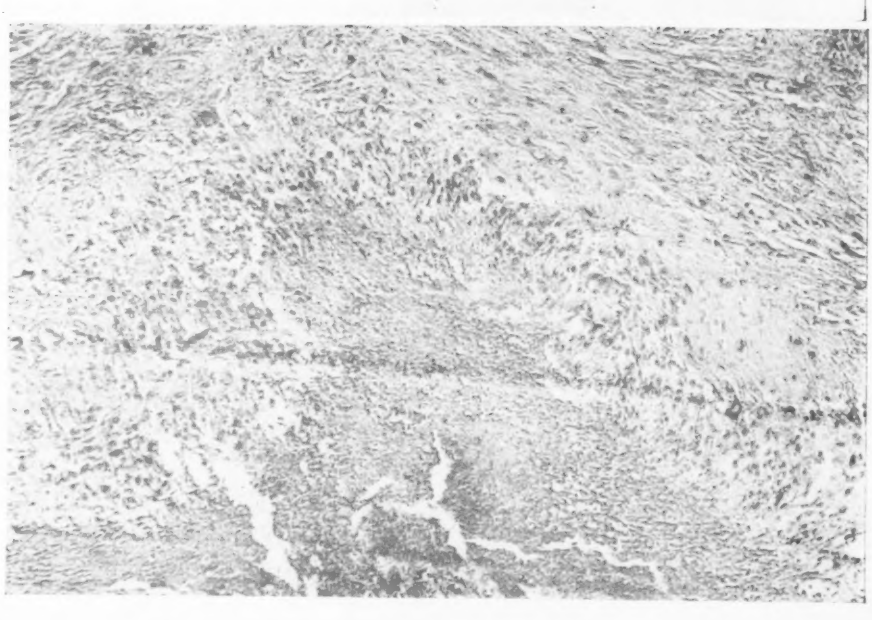

FIG. 9.—Nodule showing rheumatoid reaction in a case showing chemical, biochemical, and radiological features suggestive of gout. A focus of necrosis and fibrinoid change is seen, surrounded by radially arranged fibroblasts (Case 17).

two or three, nuclei of rounded or irregular shape. Vessels were numerous and they showed the thick, almost cuboidal endothelial lining described by Collins (1937). Throughout the whole mass there was a light infiltration with polymorphonuclear neutrophil cells. One considerable area of necrosis was present, comparable to those seen in rheumatoid arthritis, but the typical radial zone of fibroblasts was not present. The appearances were those of an acute rheumatic nodule, but it was somewhat atypical in its large size (15 mm. × 12 mm.) and the presence of frank necrosis.

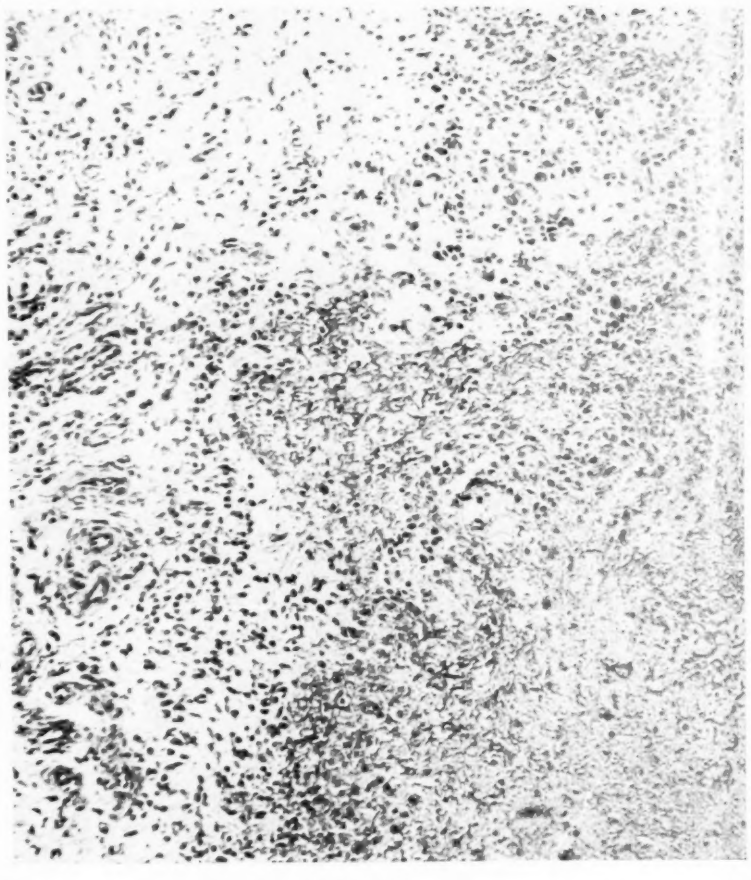

FIG. 10.—Subcutaneous nodule from a case of acute rheumatism (Case 18). An area of fibrinoid degeneration is present in young oedematous fibrous tissue. This latter is extensively infiltrated with lymphocytes, polymorphs, and undifferentiated connective-tissue cells. There are also small giant cells resembling those usually seen in the Aschoff nodule. Haematoxylin and eosin. × 100.

CASE 19

A sawyer, aged 47, gave a history of recurrent attacks of pain in back and legs of three years' duration. There was no history of past trauma or infection. He was gaining weight but still complained of generalized muscular pain. The C.S.S. and haematocrit were normal, the blood uric acid was 3·6 mg. per 100 c.cm., and the Berger test negative. Several subcutaneous nodules in the trapezius, the left upper arm and left thigh could be felt, and one of these was excised for section. The excised tissue showed skin with a lobulated fatty mass underlying it. Apart from slight congestion it showed no abnormality. Fibrous tissue was scanty, and no round-cell inflammatory reaction was seen. The nodule was lipomatous.

CASE 20

A civil servant, aged 59, gave a history of intermittent attacks of lumbago of eight years' duration. He had had a lot of domestic trouble and was not satisfied with his employment. He had spent four months in Knowle Mental Hospital. On examination there was some tenderness in the lower lumbar region, with limitation of movements of the spine. A radiograph of the spine showed slight lipping of the lumbar vertebrae. The C.S.S., haematocrit, and blood uric acid were all normal. The Berger test was negative. There were several flattened mobile tumours about 1 in. in diameter in the outer aspect of both thighs and forearms; one of these was excised for section, and was found to have the structure of a lipoma. It was quite separate from the overlying skin and was lobulated with thin fibrous capsule and septa. No inflammatory reaction was noted.

CASE 21

A woman, aged 28, gave a year's history of sudden onset of pain in the lower back. Since then she had had a dull aching pain in the lower back and neck and shoulders, with an exacerbation of symptoms during the last month. There was no history of infection or trauma. On examination the trapezii were tender, and multiple small nodules could be felt in the substance of the muscle and along the iliac crests on both sides. The haematocrit, sedimentation rate, and blood cholesterol were all normal. A small nodule deep in the gluteal fascia was excised under local anaesthesia, and was found to be an encapsulated lobule of fat about the size of a small marble (Fig. 11). Histologically it consisted of adipose tissue enclosed within a broad capsule of loose fibrous tissue. No lymphocytic or other cell-reaction was present.

CASE 22

A soldier, aged 23, who had suffered from myalgic pains for some time, was seen by Dr. W. S. C. Copeman, who had a nodule excised for examination. Dr. Copeman has kindly sent us this specimen for examination (Fig. 12). Histologically it consisted of lobulated fat enclosed by fibrous tissue. In the fibrous septa separating the fat lobules thickened vessels were seen, with some lymphocytic infiltration in and adjacent to the vessel wall, resembling that described by us (Gibson, Kersley, and Desmarais, 1946) in muscle, nerve, and joint fat of rheumatoid arthritis.

CASE 23

A private in the A.T.S., aged 21, complained of the presence of nodules which were the size of peas, soft and not tender, and were situated on the back of the hands in the region of the proximal interphalangeal joints. They had been present for two years, but varied somewhat in size, she thought with the weather. She was fit, had lost no weight, and there was no clinical joint involvement. The sedimentation rate, blood count and radiographs were all normal. A small nodule was excised

FIG. 11.

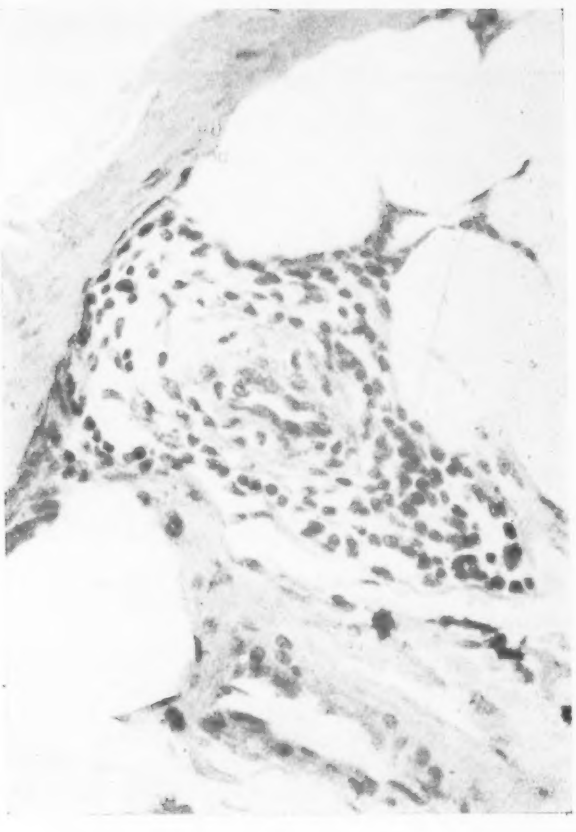

FIG. 12.

FIG. 11.—A painful nodule removed from a case of fibrositis. It consists of fat enclosed in a fibrous capsule. No round-cell reaction was seen (Case 21). Haematoxylin and eosin. × 100.

FIG. 12.—Encapsulated fat removed from the lumbar region of a case of fibrositis (Case 22). In the fat adjacent to a fibrous hand is a thick-walled arteriole with a perivascular infiltration by lymphocytes. These are also present in the adventitia and media of the vessel. Haematoxylin and eosin. × 100.

FIG. 13.—Nodule attached to the extensor tendon sheath of a digit (Case 23). It shows a simple fibrous structure of variable cellularity. No histological features of rheumatoid arthritis or acute rheumatism were present. Haematoxylin and eosin. × 50.

FIG. 13.

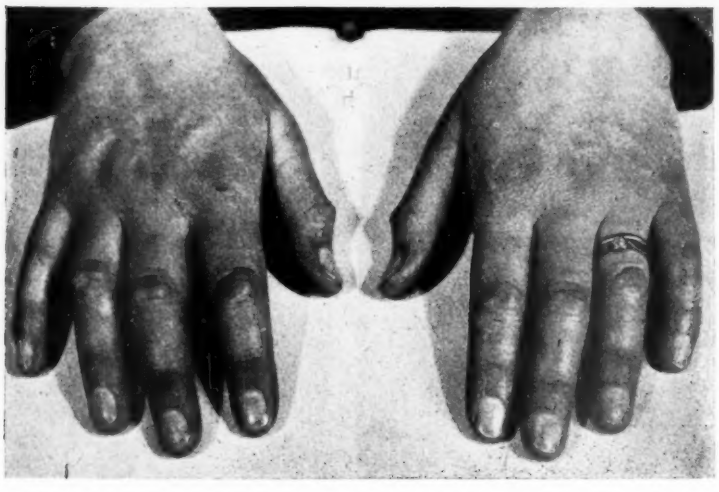

FIG. 14.—Hands of Case 27, showing fibrous nodules on the fingers. Radiographs and sedimentation rate were both normal.

and found to be attached both to the extensor tendon sheath and the overlying skin. On section (Fig. 13) it showed a fibrous structure of varying cellularity. Numerous capillaries and small vessels were present, but there was no fibrinoid degeneration or necrosis. Leucocytic infiltration was absent. This nodule had none of the features which distinguish acute and chronic rheumatism.

CASE 24

An officer, aged 33, complained of small firm nodules on the back of the hands over the interphalangeal joints of the third and fifth digits of the right hand. They had appeared gradually and were not painful, only occasioning slight stiffness. He was fit, had no rheumatic pains, and his sedimentation rate, blood count, and radiographs were normal. On excision, one of the nodules was found to be hard and attached to the extensor tendon sheath. On section it showed almost the same appearances as Case 23. It consisted entirely of fibrous tissue, in this case of rather cellular type. Capillaries were not quite so numerous as in the previous case. Again there were none of the features of rheumatoid or acute rheumatic nodules.

CASE 25

A teacher of ballet dancing, aged 47, who for twenty years had had a little osteo-arthritis of the left hip after an injury, had for the last two years two small nodules gradually forming on the extensor aspect of the proximal interphalangeal joints of the right hand. They were about the size of a pea, mobile and not very tender, but they occasioned some stiffness. The patient was not ill, and the C.S.S. (80%), haematocrit (40%), and blood uric acid (2·5 mg. per 100 c.cm.) were almost normal. A nodule was removed for section and was found to be superficial to the extensor tendon, but extending into it. On section it consisted of dense, collagenous, fibrous tissue without any inflammatory or other leucocytic reaction. Fibroblasts were scanty. In one localized area numerous small vessels were present, some with markedly thickened walls, but the nodule was otherwise avascular. The appearances were as noted in Cases 2, 3, and 24.

CASE 26

A housewife, aged 31, gave a history of generalized joint pains soon after the birth of her second child, when she was in bed for three months. Several years later, four years before her admission, her fingers became very stiff and painful and a subcutaneous nodule appeared in the left elbow, disappearing spontaneously after two years. Six months after this a large subcutaneous nodule appeared on the left elbow, but this also disappeared spontaneously. During the last year small painful and transient pearly white nodules, the size of a small pea, had appeared on the proximal interphalangeal joints of her fingers. The appearance of these had always been associated with an increase in the pain and stiffness. There had been no recent loss of weight. On examination the patient looked quite fit, and, apart from slight limitation of movement of wrists and fingers, all the other joints were normal. The sedimentation rate, haematocrit, plasma uric acid, and blood cholesterol were normal. Radiographs of the hands showed changes of gouty type. A small subcutaneous nodule distal to the proximal interphalangeal joint of the third right finger was excised for examination. Underlying the skin there was a small fibrous nodule 4 mm. × 3 mm. in size. Microscopically it consisted of fibrous tissue, with four necrotic areas of small size tending to coalesce. They consisted of an inner necrotic zone, an outer reticulated fibrinoid zone, and a cellular layer of radially arranged fibroblasts. The structure was in every way typical of the rheumatoid arthritis nodule.

CASE 27

A woman, aged 30, seen at the British Red Cross Rheumatism Clinic, Peto Place, had had some stiffness on exercise for nine years. Three years ago nodules started to appear on the proximal interphalangeal joints. They were tender and painful only during their active growth, and after this were merely disfiguring and occasioned a little stiffness. She was fit, and the sedimentation rate (8 mm.), blood uric acid (3·1 mg. per 100 c.cm. of blood), and radiographs of the hands were all normal. Fig. 14 shows the hands.

Discussion

Cases 1 *and* 2.—Cases 1 and 2 were typical of gout, both clinically and pathologically, but section of the nodule taken from Case 2 showed the presence of "foam cells" containing cholesterol (Figs. 1 and 2).

Cases 3 *to* 10.—These were typical of rheumatoid arthritis in an active phase, and the nodules excised all showed the histology now recognized as characteristic of that disease when it occurs elsewhere in the body.

In discussing the specificity of the rheumatoid nodule, Bennett (1943) went so far as to state that the subcutaneous nodule in rheumatoid arthritis, when present, was the most characteristic lesion seen in the condition, and he believed that it was easily distinguished in most cases from the nodule found in rheumatic fever. Dawson (1933) considered that the lesions were characteristic of the two diseases but represented different phases of the same fundamental pathological process. This did not mean that

the similarity of the nodules could be considered as evidence that rheumatoid arthritis and rheumatic fever were aetiologically related. Collins (1939) guardedly summed up the situation by stating that "the pathologist is not in a position to dispute the dissociation of rheumatic fever and rheumatoid arthritis", and considered that nodule formation was a non-specific reaction of connective tissue. He stated that, though fibrinoid change was a characteristic and prominent feature, he was not certain whether this change was primary or secondary to proliferation of connective tissue. He quoted Werner (1938) and Wu (1937) as proving that fibrinoid swelling of collagenous tissue might result from a non-specific stimulus, whether or not the tissues were in a hypersensitive state.

Case 11.—This patient had old, burnt out, rheumatoid arthritis, and the nodule excised showed the structure of a traumatic lesion of non-specific type.

Cases 12 *and* 13.—These were arthritics who also showed some symptoms of hypothyroidism, and in both cases cholesterol deposits were found in the nodules (Figs. 3, 4, and 5), in addition to foci typical of a rheumatoid condition. Cholesterol was also found in the nodule excised from Case 14 (Fig. 6).

Case 12 had had typical rheumatoid arthritis, with joint involvement for nine years, the nodule having been present for eight years. The blood cholesterol has been raised to 287 mg., though at the time of the excision of the nodule, when he was taking thyroid, it had fallen to 143 mg. per 100 c.cm. The blood cholesterol in Case 13 was not estimated, and the arthritis was less typical of the rheumatoid state, though the C.S.S. was decreased. The arthritis was of four years', and the nodule of eighteen months' duration.

Case 14.—Case 14 has been described previously by us (Gibson, Kersley, and Desmarais, 1946), in connexion with muscle biopsy research in rheumatoid arthritis. At autopsy a broken-down nodule in the region of the right shoulder joint consisted largely of cholesterol deposit (Fig. 6) with certain fields containing "foam cells", very similar to those seen in one of our cases of gout (Case 2, Fig. 2).

The presence of cholesterol in certain rheumatoid nodules was mentioned by Dawson (1933). Layani (1939) recorded a case under the title "rhumatisme deformant xanthomateux" which was clinically one of rheumatoid arthritis with a sixteen years' history of joint involvement with extreme disorganization. The blood cholesterol was raised, and cholesterol deposits were found in the joints and in nodules.

Parkes Weber and Aitken (1938) reported a case of arthritis of six months' duration involving the hands, hips, and shoulders, but with normal sedimentation rate and blood uric acid and with a raised blood cholesterol. Nodules were present which contained what they described as pre-xanthoma cells or multinucleated giant cells containing fat globules.

Fletcher (1946) has described a third case, a man who had had rheumatoid arthritis for eight years and nodules for four, who had a raised, though dropping sedimentation rate (70 mm. to 30 mm.) and normal blood cholesterol (135 and 154 mg. per 100 c.cm.) and blood uric acid (2·7 mg. per 100 c.cm.). Nodules showed necrotic areas containing cholesterol, surrounded by foam cells and giant cells lying between connective tissue-bundles. In some fields lymphocytic accumulations and eosinophils were also present. The larger vessels showed thickening of their walls and perivascular infiltration. He suggests that the "foam cells" are the more adult form of the pre-xanthoma cells of Parkes Weber.

In 1921 Chauffard and Troisier first described raised blood cholesterol in gout, together with amorphous cholesterol deposits in the centre of tophi and uric acid crystals at the periphery, the nodule being divided up into loculi by strands of connective tissue. It seems, therefore, that cholesterol deposition and "foam cell" formation occurs in the later stages of rheumatoid arthritis (Cases 12, 13, and 14, and those described by Layani, Parkes Weber, and Fletcher), especially when there is a tendency to hypothyroidism. In some, but not all of these cases, the blood cholesterol was raised. A similar picture can be produced in the later stages of gout (Case 2, and cases described by Chauffard).

Cases 15, 16, *and* 17 were clinically not quite typical rheumatoid arthritics; all, however, had nodules which on section were typical of this condition (Fig. 9). Each case showed "punched out" areas in the radiographs of the hands, which might easily have been taken for gouty changes, and Cases 16 and 17 clinically resembled gout. Case 16 gave the typical history of acute attacks followed by complete remissions over a period of twenty-one years. There had been no loss in weight and there was no anaemia. The sedimentation rate was only slightly increased, and the blood uric acid was normal. In Case 17 again there had been acute episodes, there was no loss in weight or anaemia, and the blood uric acid was increased to 5·0 mg. per 100 c.cm. of blood. Neither of these cases, however, reacted dramatically to colchicum medication. They represent that group of cases sometimes diagnosed as atypical gout and sometimes as atypical rheumatoid arthritis, and which appear to link together the two syndromes. They also bear out the clinical impression that radiographs in themselves are not of diagnostic value between the two conditions. They indicate the value of histological examination of nodules as an aid to diagnosis in atypical cases.

Case 18.—This case demonstrates the difficulty occasionally experienced in drawing a sharp dividing line between rheumatic fever in the adult and rheumatoid arthritis. Case 18 started exactly like an acute rheumatism, associated with carditis and both aortic and mitral lesions. Yet he did not react to full doses of salicylates, and appears to be becoming more and more like a typical rheumatoid. The nodule removed supports this view to some extent, as, while being of the type usually seen in rheumatic

fever, it was unusually large and more necrotic than is common (Fig. 10). Another feature of interest in this case is the fact that new nodules actually appeared and grew during a period when the sedimentation rate was normal.

Cases 19, 20, *and* 21.—These were cases of fibrositis. Nodules excised from the two former consisted entirely of fat (Fig. 11), bearing out the findings of Collins (1940) that biopsy of nodules on five cases of clinical fibrositis showed lipomata in three, while the fourth was a neurofibroma—the case later being confirmed as Von Rechlinghausen's disease—and the fifth showed a rheumatoid structure. This woman had some rheumatoid changes in her joints in addition to her fibrositis. Copeman and Ackerman (1944) explained fibrositis trigger points as being caused by herniation, strangulation, torsion, and oedema of fatty lobules projecting through the fascia, and they found a basic fat pattern corresponding to the common areas of tender trigger spots found in fibrositics. Our findings give some support to the view that fat may be concerned in the production of painful nodules. However, apart from the three cases quoted above, biopsy was attempted on four others. In these, nodules were palpated, but in spite of an attempt to fix them with a needle before an incision was made, no demonstrable lesion was found. This may be quoted in support of the hypothesis of Elliott (1944) that localized spasm of muscle fibres is often the cause of such tender nodes.

We can bring no evidence to support Stockman's (1920) original contention that fibrositis is due to nodes consisting of an inflammatory hyperplasia of connective tissue containing fibroblasts and serofibrinous exudate.

Case 22, from which a biopsy specimen was sent to us by Dr. Copeman, is of particular interest in that, though the nodule is essentially fatty, there are some fields where perivascular lymphocytic accumulations are present and these resemble those typically seen in rheumatoid arthritis (Fig. 12).

Cases 23, 24, 25, *and* 27.—These represent a syndrome, first described by Garrod, of subcutaneous nodules consisting of fibrous tissue attached to the extensor tendon sheath of the digits (Fig. 13). They occasioned only some stiffness of the hands, and there were no other rheumatic manifestations. The sedimentation rate, haematocrit reading, blood uric acid, and radiograph were all normal. A photograph of the hands of Case 27, seen by one of us at the British Red Cross Rheumatism Clinic, Peto Place, London, is illustrated in Fig. 14.

Case 26.—This case was in many ways clinically similar, but, though her sedimentation rate and haematocrit readings were normal, the radiographs showed some " punched out " areas and she gave a history of rheumatism in the past and also of nodules on the elbow which had come up and later disappeared. In this case the nodule excised from the finger showed, not a fibrous mass, but the structure usually seen in rheumatoid lesions.

Summary and Conclusions

Nodules from twenty-seven rheumatic cases have been examined, and biopsy performed in twenty-six of these. As a result they have been classified into five main groups according to both the clinical and pathological data available.

1. Two were cases of gout, and in the specimen from one of these, in addition to uric acid, cholesterol deposits were demonstrated.

2. (*a*) Eight cases were typical rheumatoid arthritics both clinically and in their morbid anatomy. (*b*) In two rheumatoid arthritics, who also showed symptoms of hypothyroidism, nodules excised contained cholesterol deposits both intra- and extracellular. " Foam cells " were seen in some fields. The literature on the subject of such deposits has been briefly discussed. (*c*) Nodules from three cases of atypical rheumatoid arthritis, with features clinically suggestive of gout, were shown to have the structure of rheumatoid lesions. (*d*) In one case who had had " rheumatism " but now presented no signs of active rheumatoid arthritis, an excised nodule showed this condition to be present.

3. One case of rheumatic fever in an adult, who was developing features similar to rheumatoid arthritis, had a nodule which histologically suggested rheumatic fever rather than the latter diagnosis.

4. Nodules from four cases of fibrositis were examined. Three cases showed only the structure of lipomata, but in the fourth certain areas of lymphocytic infiltration were suggestive of the lesions as found in muscle, nerve, and joint tissues in rheumatoid arthritis. However, in four other cases of fibrositis, on biopsy the nodules previously palpable seemed to have disappeared.

5. Four cases are described with fibrous nodules on the fingers and hands, but with no other clinical or pathological signs of rheumatic disease.

This study emphasizes the diagnostic value of biopsy examination of nodules in the rheumatic diseases.

We should like to express our thanks to the Sidney Robinson Research Fund for the assistance in defraying expenses in connexion with this work, and to the remainder of hospital staff of the Royal National Hospital for Rheumatic Diseases for giving us access to cases under their care.

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PLEUROPNEUMONIA-LIKE ORGANISMS AND ARTHRITIS*

BY

G. M. FINDLAY

Investigations into rheumatic diseases in man have to some extent been handicapped by the absence of spontaneous and easily reproducible arthropathies in animals. Certain strains of pleuropneumonia-like organisms now provide a means of setting up an infectious arthritis in rodents, which, though possibly unrelated to rheumatic fever and rheumatoid arthritis in man, may well serve to throw fresh light on human joint infections. A brief summary of our present knowledge of pleuropneumonia-like organisms may not be without interest.

The Pleuropneumonia-like Organisms

The first member of this group was described by Nocard and his colleagues as long ago as 1898, when they cultivated but were unable to see the causal agent of bovine pleuropneumonia.

In 1910 Bordet stained the organisms by Giemsa's method and described their pleomorphism, as also did Borrel and his colleagues (1910) who, in view of the morphology which they observed, gave them the name *Asterococcus*. The fact that Berkefeld and Chamberland filtrates were infective gave grounds for believing that these organisms could be classified among the filtrable viruses. The second filtrable organism of the group, derived from sheep suffering from contagious agalactia, was first seen by Celli and de Blasi in 1906: it was later cultivated by Bridré and Donatien (1923 and 1925). Both these organisms can be grown in a variety of media provided that a high concentration of animal protein is present.

When, after the war of 1914–18, a concerted attack was made on the filtrable viruses, attention was naturally focused on those viruses which it appeared could readily be cultivated on artificial media.

In 1934 Shoetensack in Japan isolated from dogs suffering from distemper a filtrable organism which he termed *Asterococcus canis*. Positive growth was obtained from the purulent secretions of the eye and nose, as well as from the lung, liver, and pericardial fluid. Later (Shoetensack, 1936 *a* and *b*), a second type, serologically and biologically different from type 1, was obtained from cases of distemper in dogs. Occasionally the same organisms were isolated from spontaneous pneumonia of dogs. The illustrations provided by Shoetensack, and the subsequent work of Klieneberger (1938 and 1940), on *Asterococcus canis*, leave no doubt that these organisms from dogs belong to the pleuropneumonia-like group: it is, however, very doubtful whether they play anything more than a secondary rôle in the aetiology of canine distemper.

In 1935 Klieneberger reported that a pleuropneumonia-like organism, now known as L_1, existed as a symbiont of *Streptobacillus moniliformis* (*Actinomyces muris*), with which it was found growing in culture. Since then a number of these organisms have been isolated from small rodents as well as from man and, more recently, from the developing chick embryo. What appear to be free-living members of the same group have been found by Laidlaw and Elford (1936), and by Seiffert (1937*a* and *b*) in sewage, humus, earth, and similar materials. These free-living organisms show both antigenic and metabolic differences among themselves (Pirie, 1937 and 1938), while their growth does not depend on such high protein concentrations as are necessary for the parasitic members of the group. Further investigations are required to determine the relationship of the free-living to the parasitic members of the pleuropneumonia group of organisms.

Pleuropneumonia-like Organisms from Rodents

Pleuropneumonia-like organisms have now been obtained from rats, mice, and guinea-pigs.

RATS

Many rats normally harbour *Streptobacillus moniliformis* in their nasopharynx (Strangeways, 1933) so that its symbiont L_1 (Klieneberger, 1935 and 1936) can be legitimately regarded as the first member of the pleuropneumonia-like group to be isolated from the rat. The relationship between *Streptobacillus moniliformis* and L_1 was at one period hotly debated, since some observers believed that the pleuropneumonia-like organism was merely a variant of the streptobacillus (Dienes, 1938 to 1940). The isolation of L_1 on at least one occasion from the lungs of a laboratory rat (Klieneberger, 1938) independently of *Streptobacillus moniliformis*, and the cultivation of L_1 for many generations on artificial media with no tendency to reversion to *Streptobacillus moniliformis* (Klieneberger, 1940), have shown conclusively that L_1 is itself a pleuropneumonia-like organism strictly comparable to those other members of the group which have no relation to, or association with, organisms such as *Streptobacillus moniliformis*.

In 1937 Klieneberger and Steabben obtained a

* This paper was read before a meeting of the Heberden Society on October 25, 1946. Owing to non-delivery of paper supplies and a consequent long delay in the publication of the September issue of the *Annals of the Rheumatic Diseases*, it became possible to include in it this paper, and also the account of the Heberden Society meeting held on October 25 (*see* p. 177).

pleuropneumonia-like organism, L_3, from the lungs of 17 out of 19 rats suffering from "bronchopneumonia" or "bronchiectasis". Immunologically and in other ways this organism was found to be distinct from L_1 (Klieneberger, 1938). Later, Klieneberger and Steabben (1940) examined the lungs of 251 laboratory rats and 17 wild ones. Lesions were found in the lungs of 108 laboratory rats, but pleuropneumonia-like organisms were isolated from the lungs of 138: altogether 46 out of 139 rats 8 months of age or younger yielded these organisms although their lungs were of normal appearance. Only four of these pleuropneumonia-like organisms were typed, but all were serologically similar. Among the 17 wild rats, one only showed lung lesions and only this one yielded a L_3 type organism. Efforts to produce the lesions of "bronchiectasis" in rats' lungs with cultures of L_3 have proved ineffective. Subcutaneous and intraperitoneal injections of cultures mixed with sterile agar cause abscesses: intravenous and intracerebral inoculations in mice are without effect.

L_4, the third type of pleuropneumonia-like organism from the rat, has been isolated on several occasions under somewhat different circumstances. Early in 1938 Woglom and Warren found that certain suspensions of rat sarcoma 39, when inoculated subcutaneously into rats, caused abscesses which bacteriologically appeared sterile. With Berkefeld filtrates of the pus from the abscesses the condition could be reproduced not only on subcutaneous inoculation but on intravenous injection, when there resulted widespread suppuration about the head and larger joints, the testes, and the extremities. The mouse was even more susceptible than the rat, but guinea-pigs and rabbits were insusceptible. Cytoplasmic inclusions were found in the epithelial cells of the skin in close relation to the abscesses. The causal agent was referred to as "a pyogenic filtrable virus". On culturing some of the infective material from the abscesses, however, Klieneberger (1939) showed that the responsible agent was a pleuropneumonia-like organism which serologically and culturally was identical with the L_4 organism that she had isolated in the previous year from the swollen submaxillary gland of a rat (Klieneberger, 1938). This result was confirmed by Woglom and Warren (1939). In 1939 in the rat colonies of three laboratories in London there was noted a spontaneous polyarthritis, from which a pleuropneumonia-like organism was isolated by Findlay *et al.* It was at first thought that this organism was distinct from other members of the group, but later observations showed that it was serologically identical with L_4 (Klieneberger, 1940). Somewhat earlier Collier (1938, and 1939, *a*, *c*, *d*, *e*, *f*), Collier and Esseveld (1938), and Collier and Staverman (1939), working in Java, had reported on a polyarthritis of rats which could be transmitted in series but of which they failed to isolate the causal agent. Later Beeuwkes (1940) and Beeuwkes and Collier (1942) succeeded in culturing a pleuropneumonia-like organism from the spontaneous rat arthritis, while another similar agent was obtained from rats after inoculation with blood and joint fluid from a patient suffering from acute rheumatic fever. These two strains were biologically similar, but their serological relationship to other L_4 organisms is still uncertain. The same applies to the organisms isolated by Preston (1942) and by Powell and Rice (1944) in America. The first of these American strains was obtained from a rat suffering from purulent knee joint and an ovarian abscess: other strains were obtained from the commonly occurring middle-ear infection of rats. Culturally these strains are very closely related to, if not identical with, L_4. Since a very similar condition was observed by Marshall in Nigeria in 1930 (cf. Findlay, Mackenzie, MacCallum, and Klieneberger, 1939), it is obvious that pleuropneumonia-like organisms are found in rats throughout the world. Their habitat in the normal rat is uncertain.

MICE

Pleuropneumonia-like organisms were first demonstrated in the brain of the mouse by Findlay and his colleagues (1938) in this country, while investigating lymphocytic choriomeningitis, and by Sabin (1938*b*) in America, while studying *Toxoplasma*. A similar condition had been observed some years previously in London while studying the neurotropic strain of yellow fever virus.

The L_5 organism isolated in England is closely related serologically to the type A organisms obtained by Sabin in America, although there are certain biological differences. Upon intracerebral injection of material containing the L_5 organism the mice, in from one to ten days but mostly on the second or third day, exhibit a curious rolling or turning on the long axis of the body, with or without other nervous symptoms. Some mice die, others recover in a few days, while still others exhibit a chronic hydrocephalus, with or without choreiform movements, for very long periods.

Sabin (1938*b*) showed that his type A organisms produced a neurolytic exotoxin. This organism has since been found in the brain of a normal mouse and in the conjunctiva and nasal mucosa of apparently healthy mice (Sabin, 1939*b*). Except in very young animals, L_5 organisms would seem to be normal parasites of the mouse (Sabin and Johnson, 1940*a*). Similar organisms have been obtained by Sullivan and Dienes (1939) from the lungs of mice that had had normal mouse lung suspensions instilled intranasally under ether anaesthesia.

L_6, which is distinct serologically and in its colonial growth from L_1, L_3, L_4, and L_5, was obtained from mice by inoculating them intracerebrally with blood from splenectomized mice containing the protozoon *Eperythrozoon coccoides* (Findlay, Klieneberger, MacCallum, and Mackenzie, 1939). Later Klieneberger (1940) reported the isolation by Dr. H. Jahn of a pleuropneumonia-like organism from the swollen joint of a mouse which had been inoculated with *Streptobacillus moniliformis*.

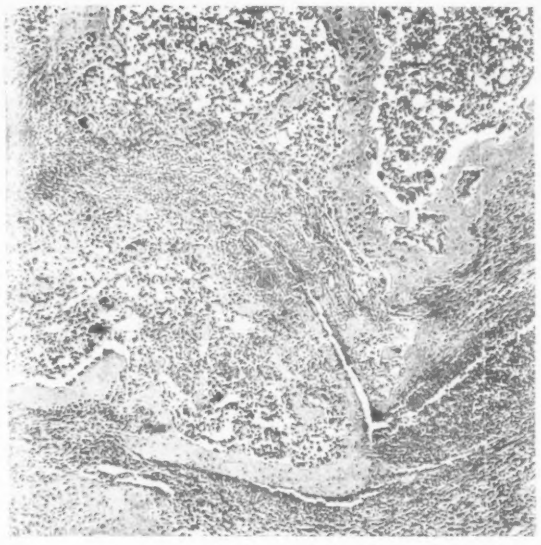

FIG. 1.—Ankle joint of mouse inoculated with L_5, showing general involvement of joint. Haematoxylin and eosin. × 100.

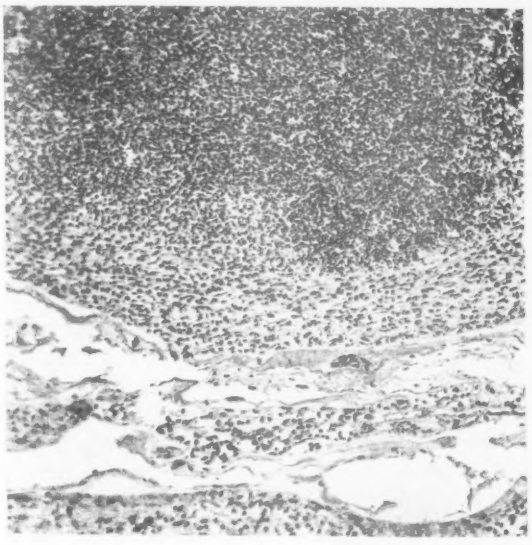

FIG. 2.—Periarticular tissue of rat inoculated with L_4, showing infiltration with polymorphonuclear leucocytes. Haematoxylin and eosin. × 150.

The organism, which is not L_1, was termed M55, but its relation to the other members of the group is uncertain.

Sabin (1938*b*, 1939*a* and *b*) and Sabin and Johnson (1940*b*) isolated a number of other strains termed B, C, D, and E from the brains, noses, and lungs of normal mice or of mice that had received intranasal inoculations of various materials. These strains do not produce an exotoxin but differ from one another serologically.

In this country Edward (1940) obtained strains of pleuropneumonia from the lungs of mice which had received intranasal instillations of mouse lung suspensions. Edward believed that pleuropneumonia-like organisms were the actual cause of the pneumonia, but it was only with the early subcultures that pneumonia was produced, and no tests were made to rule out the presence of a virus. A pleuropneumonia-like organism has been known to contaminate at least one strain of influenza virus, and, in addition, Horsfall and Hahn (1940) have found that while pleuropneumonia-like organisms may be present in the lungs of mice with a spontaneous virus-pneumonia, they are quite distinct from the latent virus responsible for the pneumonia. The writer obtained a pleuropneumonia-like organism from mice suffering from spontaneous arthritis in the Gold Coast. Unfortunately circumstances prohibited its further study. On at least two occasions rat strains have been isolated from mice. Findlay, Klieneberger, MacCallum, and Mackenzie (1939) obtained L_3 from the brain of an apparently normal mouse, while Warren (quoted by Sabin, 1941) isolated a L_4 type of pleuropneumonia-like organism from the brains of mice inoculated intracerebrally with herpes virus.

GUINEA-PIGS

Pleuropneumonia-like organisms have only once been isolated. Klieneberger (1940) obtained a strain in conjunction with *Streptobacillus moniliformis* from abscesses in the neck, but owing to war-time conditions its further investigation was impossible. Smith (1941) also obtained *Streptobacillus moniliformis* from the same type of abscess but could not separate a pleuropneumonia-like organism from the bacilli.

It is obvious that apparently normal mice and rats and, to a less extent, guinea-pigs harbour pleuropneumonia-like organisms which vary in their serological reactions and in their pathogenicity.

Pleuropneumonia-like Organisms in Man

Dienes and Edsall (1937) were the first to indicate that pleuropneumonia-like organisms might possibly be associated with man when they isolated an organism of this type from the suppurating Bartholin's gland of a woman: she had, however, been working in a laboratory with rats.

Later, in America, Dienes (1940*a*) reported the isolation of five strains from the cervices of women. Dienes and Smith (1942) published reports of the isolation of these organisms from the cervical, vaginal, and urethral secretions of women and from the urethral and prostatic secretions of man: organisms were found in 22 per cent. of 129 unselected patients. Some of the women were suffering from arthritis, some from gonorrhoea, and some from non-specific inflammatory lesions of the genito-urinary tract, while all the men were suffering from chronic prostatitis. In Australia, Beveridge (1943), Johnston and McEwin (1945), and Beveridge *et al.* (1946) have confirmed these results since they have found the organisms in both males and females with non-specific urethritis. Of 70 men with non-specific urethritis examined by Beveridge and his colleagues, 14 yielded positive results. Of 11 women who had had connexion with these positive men, only 3 yielded pleuropneumonia-like organisms. Of 101 normal women, 3 gave positive results, while 67 healthy male

medical students were all negative. Klieneberger-Nobel (1945), working at the London Hospital and the Whitechapel Clinic, obtained pleuropneumonia-like organisms from 40 per cent. of women attending the venereal disease clinic and 33 per cent. of those attending the gynaecological department for a variety of presumably non-venereal conditions: only 14 per cent. of women attending the antenatal clinic were infected. Salaman *et al.* (1946), in military personnel, found that, of gonorrhoea patients, 34 per cent. of men and 60 per cent. of women harboured pleuropneumonia-like organisms. The same organisms were common in women suffering from vaginitis due to *Trichomonas* and from non-specific cervicitis. The organisms were less common in non-specific urethritis in men, and are uncommon in prostatitis: they were found in the urethra of approximately 17 per cent. of normal men and 6 per cent. of normal women. The frequency with which pleuropneumonia-like organisms are associated with cultures of the gonococcus was originally noted by Dienes (1940*b*), and later by Brown and Hayes (1942) and Salaman (1946).

The relationship of these human strains to those of rodents has received very little attention. One unequivocal human strain studied by Warren and Sabin (1942) was not pathogenic for mice, while no evidence of toxin production was obtained. Antisera against rat and mouse strains failed to agglutinate the human organism.

These observations show that pleuropneumonia-like organisms are by no means rare parasites of the genital tracts of both men and women. Although more commonly associated with inflammatory conditions, such as non-specific urethritis and cervicitis, they were also present in apparently healthy individuals. Their isolation from human beings suffering from a particular disease does not, therefore, necessarily indicate that they are casually related to that disease.

Pleuropneumonia-like Organisms in Chick Embryos

The occurrence of a pleuropneumonia-like organism in association with a strain of influenza virus A has already been noted. More recently van Herick and Eaton (1945), in the course of passing a strain of the virus of primary atypical pneumonia amniotically in the developing chick embryo (Eaton, Meicklejohn, and van Herick, 1944), obtained a pleuropneumonia-like organism from the egg. This agent caused a sudden increase in the number of deaths of the chick embryos and was characterized by the appearance of small, opaque areas as well as by small white granular thickenings on the amniotic membrane, in which there was an abundance of organisms. The amniotic fluid was cloudy and the embryos often stunted. Woglom and Warren (1938), and Findlay, Mackenzie, MacCallum, and Klieneberger (1939) had already shown that L_4 would readily grow in the developing chick embryo.

The egg-passage pleuropneumonia-like organism when injected into chickens caused a transient weakness of the legs 26 days after inoculation with, in the case of one of the chickens inoculated intranasally, tremors and ataxia. Cotton rats (*Sigmodon hispidus* sp.), when injected intranasally, showed a red oedematous consolidation of the lungs. Filtrates which were sterile when inoculated into serum broth produced similar lesions. The toxin causing pulmonary haemorrhage and oedema in cotton rats was thermostable and, as indicated by preliminary experiments, non-antigenic.

Sabin (1938*b*) had found that his type A organism from mice produced a true neurotropic exotoxin which gave rise to choreic movements. This toxin was thermolabile, antigenic, and neutralizable with an immune serum: even earlier Nocard *et al.* (1898) had obtained evidence of the production by the organism of bovine pleuropneumonia of a soluble substance toxic for rabbits.

The pleuropneumonia-like organism isolated by van Herick and Eaton was found to agglutinate chick red cells, as do influenza, Newcastle disease virus, vaccinia, and fowl plague virus: in addition, sera from year-old fowls from the hatchery which had supplied the eggs used in the virus investigation showed the presence of appreciable amounts of antibody against the pleuropneumonia-like organism. There is, therefore, a strong presumption that pleuropneumonia-like organisms may exist in the normal fowl. In view of the large number of different vaccines now prepared in the developing hen's egg, the isolation from eggs of pleuropneumonia-like organisms which are filtrable is a matter requiring further attention.

Characteristics of the Pleuropneumonia-like Organisms

The pleuropneumonia-like organisms form a very definite group, but their exact systematic position is still somewhat uncertain. Borrel and his associates (1910), using dark-field examinations and Loeffler's flagellar stain, saw in the organism of bovine pleuropneumonia not only granules and round forms, but long branching filaments, extending in some cases in many directions from the round forms. The name *Asterococcus* appeared to be appropriate. Turner (1935) in dark-field preparations observed the multipolar germination of the round forms. The majority of observers, including Klieneberger and Smiles (1942), believed that the pleomorphism, the growth in branching filaments, the particular softness, and the special manner of reproduction, differentiate these organisms from the bacteria. Turner (1935) in fact placed them in a new order, *Borrelomycetales*, Sabin in a new class, *Paramycetes*. The suggestion by Ledingham (1933) that they should be classified with the *Actinomycetaceae* was not considered by later observers, nor was the still earlier suggestion by Bordet (1910) that the pleomorphism of bovine pleuropneumonia might be analogous to the pleomorphism of certain bacterial cultures.

It is now generally agreed not only that the

morphology of all the pleuropneumonia-like organisms is very similar, whether they are parasitic or free-living, but that they cannot be regarded as growth forms of *Streptobacillus moniliformis* or of the other organisms with which they are often found in artificial culture media. The most recent observations by Weiss (1944), Dienes (1945 and 1946) and Smith *et al.* (1946), employing both stained preparations and the electron microscope, show that in young colonies pleuropneumonia-like organisms, whether isolated from rats, mice, or man, appear as small bacilli with bipolar staining. The bacillary forms round up and may swell to large size. These large round forms either develop vacuoles and degenerate into empty blebs, or reproduce small bacillary forms inside their membranes. Occasionally freshly isolated strains of certain common bacteria, such as *Haemophilus*, are known to swell into round forms of variable size, reproducing the small forms again, as do rickettsiae and certain viruses, such as those of lymphogranuloma venereum and psittacosis. The pleuropneumonia-like organisms are, it is suggested, intermediate between small Gram-positive organisms, such as *Pasteurella* and *Haemophilus*, and these viruses. Smith *et al.* (1946), with the aid of the electron microscope, distinguished spherical forms, short filaments, and many rod-shaped forms which show the structure characteristic of bacilli in that they are provided with a cell wall and intracellular granules lying within the cytoplasm. These observations tend to suggest that the branching of the filaments stressed by earlier observers such as Turner (1935) is an artefact. Klieneberger and Smiles (1942) and Dienes (1945) believe that the filaments are due to the stretching of the round forms. The morphology of the pleuropneumonia-like organisms is thus comparatively simple, since small, " elementary " corpuscles either multiply as such or swell up to large forms which again break up into elementary bodies.

Pleuropneumonia-like organisms do not take Gram's stain but are readily coloured by Giemsa's method. They give a positive reaction for nucleic acid by the Feulgen technique. Many, but by no means all, strains of pleuropneumonia-like organisms require an adjuvant such as sterile agar or a suspension of cells in order to set up infection when injected into animals. In size, as shown by filtration through gradocol membranes, pleuropneumonia-like organisms, or rather the granular forms, vary from 125 to 250 mμ. They are non-motile, are readily destroyed by heat, and have no specific resistance to glycerol.

Pathological Changes

There is still much to be learnt about the pathogenicity of organisms of the pleuropneumonia group. While the organisms of bovine pleuropneumonia and contagious agalactia are definitely pathogenic for certain ruminants, the organisms isolated from rats have been found pathogenic only for rats and mice, while those obtained from mice are either non-pathogenic or pathogenic only for the same species. Apart from one strain which, as previously mentioned, was not pathogenic for rodents, the pathogenicity of human strains either for man or for rodents is unknown. Much further work requires to be done on the possible pathogenicity of human strains for rodents.

The three free-living strains, A, B, and C, isolated by Laidlaw and Elford (1936) showed no pathogenicity for rats, mice, or rabbits, and serologically were distinct from available parasitic strains (Klieneberger, 1940).

In the case of bovine pleuropneumonia, it is well known that in the later stages of the disease inflammatory arthritic changes may occur, while injections into the root of the tail of sucking calves or of reindeer causes an inflammation of the joints. Intracerebral injection into cows is also said to cause invariably an inflammation of the joints. Meyer (1910) believes that in adult cows the tendency to produce arthritic changes after prophylactic tail inoculations was not due to individual predisposition but to the particular strain of organism. The power to produce arthritic changes was lost by continued passage either in animals or in artificial media, and no secondary joint affections could be produced subsequently by inoculation of cultures.

In contagious agalactia of sheep, in addition to a mastitis and a conjunctivitis, an arthritis is by no means uncommon. According to Pigoury (1938), arthritis occurs in 10 to 20 per cent. of goats, coming on usually about a week after the beginning of the disease. One joint alone is usually affected, generally that between the radius and the carpus, more rarely the tibio-femoral, the tibio-astragaloid or the metacarpals. The symptoms vary from simple stiffness to acute arthritis with complete functional incapacity. Spontaneous cure generally takes place after one or two months, but in some cases ankylosis is complete, with abscess formation involving the articular surfaces. In the chronic form of the disease there may be remissions and exacerbations of the arthritis without ultimate deformity. Some generalized wasting of the muscles is common. The process in the mammary gland is that of an interstitial mastitis with disappearance of glandular tissue: in the eye there is an interstitial parenchymatous keratitis with infiltration of small cells and vascular proliferation. In the rat, L_4 strains cause abscess formation when inoculated subcutaneously. After intravenous injection death may occur in a few days without any joint involvement, but if the animal lives one or more joints become affected. The first sign in an affected joint—usually the tibio-tarsal, radio-carpal, intertarsal, or phalangeal—is swelling with a glistening, smooth, pearl-coloured appearance of the skin. Later, the whole region of the joint takes on a pink or even purplish tint and is slightly oedematous. This condition may eventually subside leaving only some slight thickening, or, while the joint is still swollen, the skin may ulcerate: gangrene of the limb may then result. Histologically the inflammatory lesions are at first periarticular

with an infiltration of polymorphonuclear leucocytes: abscess formation occurs, involving the capsule, synovial membrane, and, at a later stage, bone and cartilage. A considerable exudate may be found within the joint capsule, while the cartilage is uninvolved. As the disease progresses, cartilage is sooner or later destroyed by a rapid necrotizing process: osteomyelitis may occur.

In the affected joints there is considerable cellular infiltration and thickening of the periarticular connective tissue but no involvement of cartilage or synovial membranes. Sometimes, however, there is erosion of the articular cartilage or the formation of polypoid growths of newly formed connective tissue. Endarteritis is described in the joint tissues by Carré (1912).

In mice infected with organisms of the L_5 type, the arthritic changes are very similar in character to those produced by L_4 but involvement of the articular cartilage is very rare and complete recovery occurs without ankylosis. With organisms of his type B group, Sabin (1940) found that the articular changes are more widespread and involve all the joint structures. The changes are essentially proliferative in character and come on within 24 hours of inoculation. The capsular tissues, synovial membranes, and perichondrium are later involved, so that obliteration of the free joint space is common. Destruction of the cartilage is seen later, but not until at least four weeks after intravenous injection: the normal articulating cartilage may be replaced by immature chondroblasts or osteoblasts, and in an ankylosed joint there may be considerable ossification in the distorted articulating surfaces, which are joined by dense fibrous tissue.

Pleuropneumonia-like organisms of the L_5 type when injected intracerebrally cause an intense inflammatory reaction in the brain, together with neurolysis of many cells. When injected into the pleura or peritoneum there are no local lesions, but an exotoxin is produced which causes both a disintegration of the posterior pole of the cerebellum and degenerative non-inflammatory changes in the cerebral cortex, basal ganglia, and nervous part of the retina (Sabin, 1938*b*). True cytoplasmic inclusion bodies do not appear to be formed by pleuropneumonia-like organisms but the presence of the organisms in the cytoplasm of macrophage cells may sometimes be demonstrated. In mice inoculated with some strains a conjunctivitis is not infrequent.

It will be seen that certain strains of the pleuropneumonia-like organisms have a predilection for joint structures: they may cause an acute suppurative arthritis or a more chronic proliferative change somewhat akin to that of rheumatoid arthritis in man. Much further work requires to be carried out on the pathogenicity of these organisms.

Chemotherapy

Earlier investigators apparently obtained beneficial action in contagious agalactia by the injection of the sodium salt of acetarsol (3-acetylamino-4-hydroxyphenylarsonic acid) which, according to Bridré *et al.* (1928), exerts a preventive and curative action in the disease both as it occurs naturally and as it is experimentally produced in sheep or goats. Pigoury (1938) found that a single dose of 0·75 gr. had a therapeutic effect on the course of the mastitis and arthritis. Of 27 treated animals, all showed improvement, while in 30 controls either untreated or merely given urotropine the disease ran its normal course. A single dose of acetarsol protected an animal against infection for a week. Witt (1925) observed some beneficial action of arsenicals in bovine pleuropneumonia. Arsenicals have not, however, come into general use for the treatment of these infections in domestic animals. With the spontaneous rat arthritis due to L_4, Collier (1939*b* and *g*), who was then unaware of the causal agent, found that aurothioglycose (Solganal B) was capable of preventing the development of the arthritis. Later, working with known strains of L_4, Findlay, Mackenzie, MacCallum, and Klieneberger (1939) and Findlay, Mackenzie, and MacCallum (1940) confirmed the preventive action of sodium aurothioglucose (Solganal B), and found that other organic gold compounds, such as sodium aurothiomalate, lopion, parmanil, and neosolganal, were also effective. If treatment with 10 mg. of sodium aurothioglucose per 20 gr. of body weight was delayed till 48 hours after inoculation of the organism there was evidence of curative action in mice, none of the treated mice being dead in 96 hours after infection while in the untreated series 6 out of 24 were already dead. When the administration of aurothioglucose was delayed till four or five days after infection, there appeared to be some slowing up of the infective process. In mice which had been successfully treated with gold compounds, no pleuropneumonia-like organisms could be isolated subsequently from the affected joints. The same was true when organic gold compounds were used to treat an infection due to *Streptobacillus moniliformis* associated with a pleuropneumonia-like organism obtained from guinea-pigs.

Apart from organic gold salts, neoarsphenamine was found to have a slight action in preventing the development of arthritis in mice due to L_4 while neoarsphenamine, acetarsol, and, to a less extent, tryparsamide had also a slight action in preventing the nervous symptoms in mice due to L_5 organisms. No action could be detected on rodent pleuropneumonia-like organisms of sulphanilamide, sulphapyridine, sodium salicylate, and lithium antimonyl tartrate. Sabin and Warren (1940*a*, *b*) tested the action of organic gold salts on the arthritis caused in mice by their type B organism: here the curative action was more in evidence. A new compound, calcium aurothiomalate, was claimed by them to be practically non-toxic in mice and yet to produce a curative action even after a single dose of 1 mg. With type B organisms Sabin and Warren failed to find any bactericidal action by gold salts *in vitro*. With L_4 cultures there appeared to be a zone effect, the bactericidal action depending on the

concentration of sodium aurothioglucose (Findlay *et al.*, 1940). A similar zone phenomenon has been found by Courmont *et al.* (1932) and by Pichat (1939) in connexion with the bactericidal action of gold salts on tubercle bacilli. Preston (1942), and Powell and Rice (1944) have also found that sodium aurothiomalate was quite effective in rat arthritis due to L_4, although owing to its toxicity its administration was hazardous. The latter observers found that penicillin was ineffective: similar results have been obtained in this country.

More recently Powell *et al.* (1946) have shown that streptomycin is highly effective if started shortly after infection. For rats of 100 g. body weight, 3,000 units a day for three days was preventive, the daily dose of 3,000 units being given in three doses each of 1,000 units. In another experiment, with a total of 36,000 units per rat spread over four days in three doses a day, 8 out of 10 rats were entirely free from infection while 2 others showed a questionable and transitory trace of swelling in one toe for two days. The 10 control rats were all dead in three weeks.

It is perhaps of interest to note that bile salts have some action on the development of experimental arthritis in rats. Snow and Hines (1941) found that ligation of the common bile duct of rats before or 20 hours after the injection of L_4 organisms delayed the onset and decreased the degree of arthritis. No similar effect was produced when an arthritis was set up with streptococci.

The Relationship of Pleuropneumonia-like Organisms to Human Diseases

With the discovery that pleuropneumonia-like organisms are the cause of arthritic conditions in cows, sheep, goats, rats, and mice, the question naturally arose whether these same organisms might not be responsible for arthropathies in man. Swift and Brown (1939) in fact claimed to have isolated pleuropneumonia-like organisms from patients with rheumatic fever. They subsequently agreed, however, that their direct "cultures" had been misinterpreted while the strains obtained after passage through mice were biologically and immunologically identical with those normally carried by these animals (Sabin 1939*a*).

Subsequent attempts by a number of investigators to cultivate pleuropneumonia-like organisms from joint exudates and from the tissues of patients with rheumatic fever or rheumatoid arthritis have all failed (Sabin, 1939*a*; Sullivan and Dienes, 1939; Findlay *et al.*, 1940; Sabin and Johnson, 1940*a*; and Preston, 1942). At present, therefore, the direct relationship of pleuropneumonia-like organisms to rheumatic fever and rheumatoid arthritis must remain non-proven. Further investigations might, however, be undertaken to determine whether streptococci isolated from rheumatic joints are ever contaminated with the pleuropneumonia-like organisms: in addition the effects of infecting streptococci into joints already infected by pleuropneumonia-like organisms appears worthy of study.

Apart from the possible relationship of pleuropneumonia-like organisms to non-specific urethritis, there appear to be two human diseases where further investigation of the rôle played by pleuropneumonia-like organisms might be worth while. These diseases are Haverhill fever and Reiter's syndrome. Haverhill fever is one of the two forms of rat-bite fever: it is characterized by fever and polyarthritis and is usually thought to be due to *Streptobacillus moniliformis*, which has been cultivated from the blood (cf. Farrell *et al.*, 1939). In view of the frequency with which pleuropneumonia-like organisms are associated with this bacillus, the question arises how far the symptomatology in man is due to an associated pleuropneumonia-like organism and how far to the *Streptobacillus*. All cases of rat-bite fever should, when possible, be investigated for pleuropneumonia-like organisms. *Streptobacillus moniliformis*, however, is very susceptible to penicillin, while the evidence at present suggests that pleuropneumonia-like organisms are not.

The second human infection for which there is reason to think a pleuropneumonia-like organism may be responsible is Reiter's syndrome, originally described in Germany in 1916, and characterized by the triad of polyarthritis, urethritis, and conjunctivitis. Efforts should be made to culture pleuropneumonia-like organisms from the conjunctiva, joints, and urethral discharge of all patients suffering from Reiter's disease. Unfortunately, complement fixation tests with cultures of human pleuropneumonia-like organisms have not, up to the present, proved highly specific: however, there is some evidence that skin sensitivity tests may be of greater value in diagnosing those who are suffering from an active infection due to pleuropneumonia-like organisms.

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THE NATURE OF FIBROSITIS

III. MULTIPLE LESIONS AND THE NEURAL HYPOTHESIS*

BY

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Essential to the view of fibrositis presented in this and in the preceding two papers (Kelly, 1945, 1946) is the concept of the deep pain system. Sir James Mackenzie (1920), whose views upon pain-spread have been supported and amplified by the most recent advances, was not in possession of the knowledge which separates the cutaneous from the deep pain system. But he asserted repeatedly that, when pain is referred from a viscus to the abdominal wall, deep rather than superficial hyperalgesia is likely to result. Lewis and Kellgren (1939) were the first to demonstrate that the two pain systems are anatomically separate; though Head, Rivers, and Sherren (1905) had pointed out that the paths which conveyed deep pressure-pain travelled with the motor nerves.

Clinically, there is a great deal of evidence suggesting such a functional division. Thus, pressure-pain normally is not abolished by section of a sensory nerve (Trotter and Davies, 1909; Sharpey-Schäfer, 1927; Seddon, 1943). When anaesthesia occurs in interstitial neuritis, the deeper tissues usually present normal or even enhanced sensitivity to pressure; this phenomenon is characterized by the term " anaesthesia dolorosa ". There is much in Head's differentiation of protopathic from epicritic sensation which suggests that he was groping towards this more fundamental division.

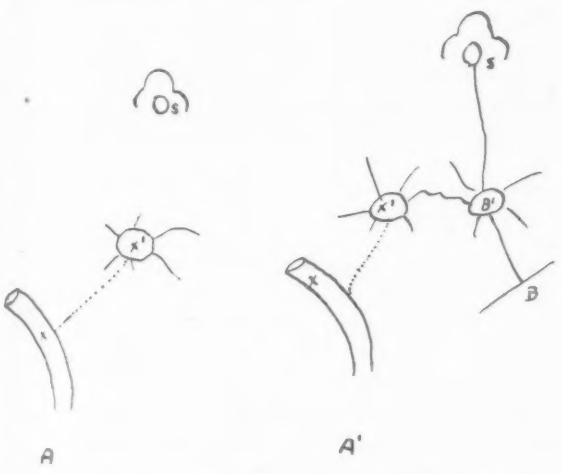

FIG. 1.—(After Mackenzie, *Symptoms and Their Interpretation.*)

A.—" The normal movements of a viscus, X, pass into the central nervous system, X′, but produce no sensation."

A[1].—" Shows the mechanism of a viscerosensory reflex. A stimulus arising in a diseased organ, X (as in gastric ulcer), passes into the central nervous system, X′, and if the stimulus be of a particular quality or strength it will affect a neighbouring sensory cell, B′, will be recognized as pain, and referred to the peripheral distribution of the nerve at B."

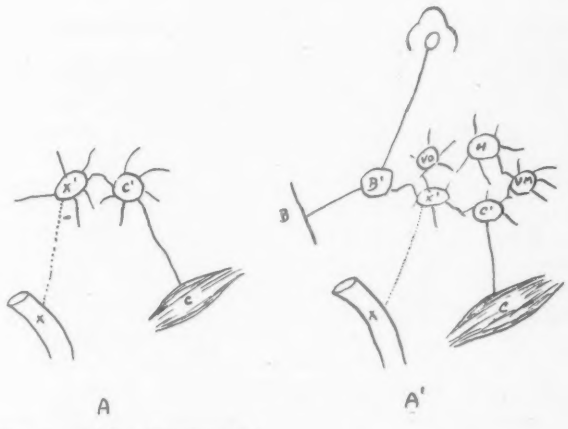

FIG. 2.—(After Mackenzie.)

A.—" Shows the mechanism of the viscero-motor reflex. A stimulus arising in a diseased organ, X, passes into the central nervous system, X′, and affects a neighbouring cell, C′, which causes a contraction of skeletal muscle."

A[1].—" Illustrates the mechanism of multiple reflexes produced by visceral stimulation. An adequate stimulus arising in an organ, X, passes to X′ in the central nervous system and affects a series of neighbouring cells, thus giving rise to pain (by stimulating B′), muscle contraction (by stimulating C′), vomiting (by stimulating the centre for vomiting, VO), cardiac depression (by stimulating the vagus, H), pallor and sweating (by stimulating the vaso-motor centres, VM)."

Myalgic Lesions and Visceral Disease

In the second essay of this series, the development of a myalgic lesion from visceral disease was traced. The first step was the appearance of secondary or referred deep tenderness; and a spot in this affected area later became an autonomous lesion with its own secondary effects. The late Sir Thomas Lewis (1942) insisted that the mechanism of referred pain from somatic lesions did not differ from that of visceral referred pain; and so it was suggested that the same mechanism was employed when a fibrositic lesion formed in response to injury to somatic tissues.

Mackenzie's concept of the irritable focus in the cord was an accurate one, in that the spread of pain

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depends upon an area of heightened reflex activity; but he was not aware of the part played by reflex antidromic activity. Thus he suggested that tenderness in response to visceral disease was more apparent than real, normal impulses being modified while en route to the cerebrum because they had to pass through the irritable focus (see Fig. 1). The muscular rigidity he held to be the result of a true reflex (see Fig. 2), as were the numerous concomitants of severe visceral pain. " The hypersensitive or hyper-irritable focus of Mackenzie ", wrote Hinsey and Phillips (1940), " takes on real meaning if we assume that both somatic and visceral afferent fibres carry impulses which affect a common pool of secondary neurones and that the principle of summation and inhibition are applicable." Add to this the concept of the bi-directional conduction of impulses, which was not accepted in Mackenzie's day; impulses normally travel " antidromically " in sensory nerves, and an excess of reflex antidromic stimulation may be responsible for many of the painful manifestations of disease.

The tenderness in the abdominal wall, therefore, signifies a true physical change resulting from reflex stimulation through deep sensory neurones, and the state of affairs can be depicted as in Fig. 3. The reflex possesses an efferent arc even as the motor reflex does, and a relay through a second deep sensory neurone is necessary in order to transmit the sensation of tenderness to the cerebrum. In Fig. 3 is portrayed also the reflex production of muscular rigidity and cutaneous hyperalgesia, and a possible version of the manner in which a myalgic lesion arises. A part of the muscle (perhaps related to the muscular sense organs) may develop the features of a myalgic lesion, with the capacity to produce reflex secondary effects. After the cure of the visceral disease this lesion may endure, producing signs and symptoms resembling those of the disordered viscus.

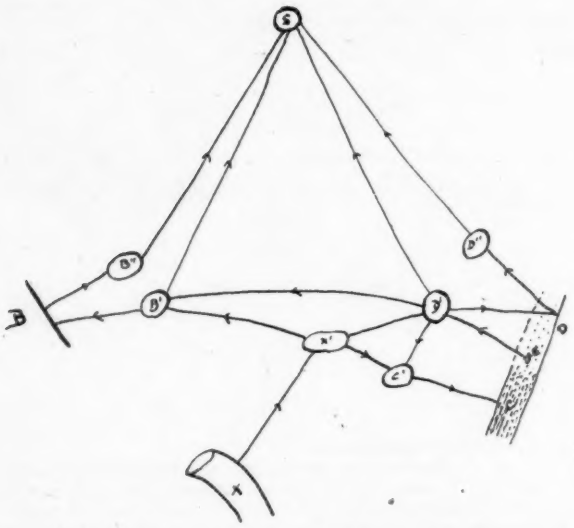

FIG. 3.—Illustrates, in the manner of Mackenzie, the present conception of the mechanism of the reflex spread of deep sensory and motor effects from a diseased viscus or from a myalgic lesion.

(1) The stimulus from X passes to X′, and, if adequate, stimulates a cell of deep pain sensation, D′, a motor cell, C′, and, less commonly, a cell of cutaneous sensation, B′. Antidromic impulses travel from D′ to D, where the deep pain receptors are situated, and deep pain and hyperalgesia result, which are transmitted to a second deep sensory cell, D″. Impulses from both D′ and D″ are recorde dat S as deep pain. Similarly, antidromic impulses from B′ activate pain receptors in the skin and give rise to cutaneous hyperalgesia and pain which are transmitted to a second sensory cell, B″. Impulses from B′ and B″ are recorded at S as cutaneous pain. A spot, E, in the hyperalgesic deep tissues, becomes acutely tender and gives off painful impulses on its own account, the resultant symptoms closely resembling those of the visceral disease.

(2) Eliminating X and X′, the diagram illustrates how a myalgic lesion, E, may give rise: (i) to diffuse deep tenderness: E to D′ to D to D″ to S; (ii) to muscular rigidity: E to D′ to C′ to C; (iii) to cutaneous hyperalgesia: E to D′ to B′, etc.

Spread from Injured Somatic Tissues

When the formation of a myalgic lesion follows an injury, the process is analogous. The lesions show a tendency, as though under the influence of some unknown law, to develop in certain " sites of election ", which often are in the region of musculotendinous junctions. So frequently does this happen that it must be assumed that these sites have some functional connexion with the central nervous system. In Fig. 4 is attempted the portrayal of the development, in response to an injury to a digit, of a myalgic lesion in the upper part of the forearm, which causes a secondary radiation of pain back to the extremity (see Cases 10 and 15, Paper II).

A number of these " sites of election " are scattered through the somatic tissues, and they seem to have a strange affinity with the painful sequelae of injury, and indeed with all fibrositic processes (see Fig. 1 and the accompanying table in Paper II, 1946). When somatic pain begins to spread, it is as the result of heightened reflex activity in the cord, or the facilitation of nervous pathways; and a number of common sites may be involved together or in succession. At each of these sites the lesion

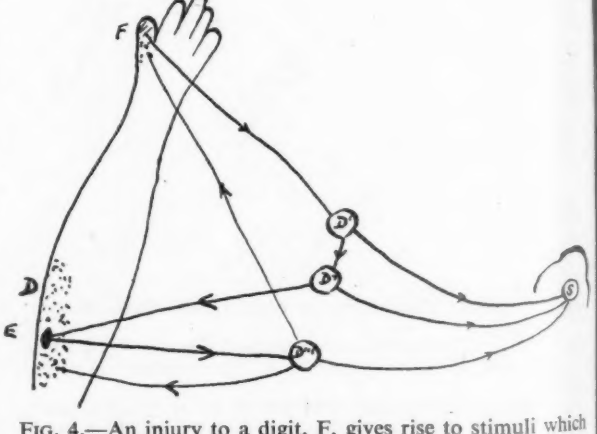

FIG. 4.—An injury to a digit, F, gives rise to stimuli which pass to a sensory cell, D′. If the stimuli are adequate, a second sensory cell, D″, is involved, which sends antidromic impulses to a " site of election," E. The resultant myalgic lesion establishes connexion with a third cell, D‴, which by antidromic stimulation causes diffuse deep tenderness, D, and stimulates pain receptors at F, the site of the original injury. When the wound at F heals, the persistence of the lesion, E, results in the persistence of pain and tenderness at D and F.

will produce its characteristic secondary effects (muscular stiffness, diffuse tenderness, pain radiating to joints, etc.). Fig. 5 suggests a possible mechanism by means of which this spread takes place. "Excitation in a pool of neurones", said H. S. Gasser (1937), "is dependent upon everything which is taking place in the nervous system." And in its capacity for facilitating the spread of pain, the deep pain system sometimes behaves like a confluent pool of neurones. There is, however, a basic division into segments which do not correspond with the dermatomes (Kellgren, 1938, 1939; Lewis, 1942).

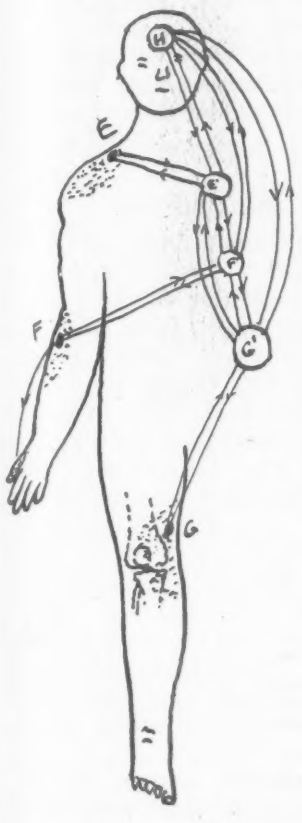

FIG. 5.—Illustrates the spread of the rheumatic process through a pool of sensory neurones. The sites of election, E F, G, appear to have special functional relations with groups of internuncial sensory cells, E′, F′, G′. These groups are linked with each other and with higher centres (H). Heightened reflex activity anywhere in this pool of neurones is capable of causing antidromic stimulation of E, F, G, with resultant local secondary effects (peri-arthritis of shoulder, pain referred to hand, synovitis of knee). Also, disordered activity of higher centres, H, may lead in similar fashion to somatic manifestations.

Multiple Lesions Resulting from Injury

In diseases which are undoubtedly rheumatic, the formation of multiple lesions is acknowledged to be common. Quite frequently, also, a post-traumatic lesion progresses to the formation of a number of metastatic lesions. It is surprising that this phenomenon earns such scanty comment; for a wealth of such examples will be seen by the clinician who keeps on the alert for them. They are difficult to explain except as the effects of reflexes set off by the trigger mechanism of the injury. It is customary to assume the existence of an inherent predisposition to rheumatism. Douthwaite (1945) has quoted Ryden, who reported 19 cases in which rheumatic polyarthritis followed an injury to a single joint. In some of the cases reported by Ernstene and Kinell (1940), coronary occlusion was followed by peri-arthritis of the left shoulder, and later by rheumatoid changes in many joints.

Case Reports

CASE 1

Lumbar backache and "sciatic" pain following traumatic Achilles bursitis.—The rubbing of his boot caused a soldier's left heel to become painful. Four weeks later his back began to ache, and two weeks after this he felt a pain in the buttock which would radiate down the back of the thigh. Examination revealed a swelling at the insertion of the tendo calcaneus; there was also (1) a myalgic lesion in the left erector spinae muscle at the level of the fourth lumbar vertebra which caused painful limitation of flexion of the lumbar spine; (2) a lesion near the centre of the left gluteus maximus, with painful spasm of the hamstrings on straight-leg-raising. An injection of procaine into each lesion completely relieved both disabilities. Though the backache recurred, the "sciatica" did not return.

CASE 2

Multiple fibrositic lesions after injury to knee.—Gnr. T. R. had his right medial meniscus removed in Sept., 1940, following an injury to the knee earlier in the year. The knee remained painful, and the pain later extended to the hip. In Feb., 1942, he complained, in addition, of (1) "sciatica" of six months' duration (pain in the right buttock would shoot down to the popliteal space and to the calf), and (2) a pain in his right shoulder, of three months' duration, made worse by moving his neck or abducting his humerus. On examination of the leg, pain was felt in the thigh and calf on attempting straight-leg-raising, but there was no cutaneous sensory abnormality or diminution of the ankle-jerk. A tender spot was found in the hamstring muscles 4 inches below the tuber ischii; deep infiltration with procaine completely abolished the disability; but it recurred when the analgesia passed off. The shoulder, however, was treated with complete success by the injection of a few c.cm. into a "supraspinous spot".

Bilateral Symmetry

To Sir James Paget (1879) the exact symmetry of many rheumatic lesions offered proof of the existence of a neural mechanism. "It is clearly", he wrote, "more probable that the symmetrical distribution of diseases on corresponding portions of the upper and lower extremities should depend on central nervous relations rather than on any assumed identity of chemical constitution." Livingston (1943) wondered at the paucity of medical comment on this frequently observed phenomenon.

When the present writer had produced in himself a painful artificial lesion of the muscles of the right calf (see Paper I), pain and deep tenderness extended up into the thigh and down to the commencement of the tendo calcaneus. On the following morning a pale reflection of the pain was felt in exactly corresponding regions of the left leg, and these areas were tender to pressure. Some weeks later, the left biceps brachii was treated in the same way, and on the following day both arms ached in regions which corresponded exactly. Two weeks after this, when another lesion had been produced in the left gastrocnemius, the right arm was painful and tender for a few hours in the identical region to which the pain previously had radiated from the left biceps. If this last observation has any significance, it suggests that the paths through which pain impulses must travel are subject to facilitation; and also that the impulses frequently do not confine themselves to the segments in which they originated.

In Case 9 (Paper II), long-standing pain in both hands was cured by means of an injection of procaine into the left forearm. The following case is representative of a number in this series.

CASE 3

A soldier gave a history that in a cycle accident six years previously he had injured the knuckle of the right third metacarpal bone. There was no disability; but five years later he began to suffer intermittently from an aching pain in the metacarpo-phalangeal joint. When seen by the writer he had " reported sick ", with a painful swelling of the third metacarpo-phalangeal joint of each hand. There was no radiological abnormality, and the disability subsided within ten days.

Fibrositis and Febrile Illness

Copeman (1943) has pointed out that tender spots may persist in the muscles after such illnesses as respiratory tract infections, later to assume abnormal activity as fibrositic lesions. This calls to mind the transient bodily pains in influenza and other infectious diseases, which may persist into convalescence as fibrositis. Copeman (1944) further described some cases of multiple fibrositis in the desert (in reality they amounted to mild rheumatic fever), in which the precipitating cause was exhaustion, exposure, furunculosis, malaria, sand-fly fever, dysentery, and other non-streptococcal infections. In the pandemic of rubella of 1940, multiple fibrositic or polyarthritic lesions were a common sequel. Case 4 is an example.

CASE 4

Mrs. L. F. had pains in her hands, knees, and ankles after German measles. The hands were swollen and the fingers stiff. The ankles were tender and slightly puffy; the site of swelling, which was mainly periarticular, was in the knees, the right being worse than the left. After a week, careful examination of the right knee revealed: (1) stiffness of the joint, which could not be flexed more than 80 degrees; (2) deep tenderness posteriorly, spreading over the lower third of the thigh and the upper third of the calf, and extending forward over the inner aspect, to the inner half of the anterior aspect of the joint; (3) swelling, mainly periarticular, in front and on the inner aspect of the joint, with some induration over the internal condyle; (4) a spot of acute tenderness was detected at the upper border of this indurated area (Fig. 6). A deep infiltration here caused all the tenderness to disappear, and the knee could be flexed fully. No more pain was felt in the knee, and the swelling subsided within 24 hours; but the joints which had not been treated remained painful and swollen for a week.

Case 4 was significant, for it demonstrated that a soft-tissue lesion could be responsible for acute rheumatic arthritis of the knee. The lesion was situated at the common " site of election " for the knee, as reported in a previous paper (Kelly, 1944*a*). Case 4 presented all the features of mild rheumatic fever; and one is reminded that Copeman, in his study of rheumatic fever in the desert, frequently observed painful swelling of joints to spread from fibrositic lesions in adjacent structures.

Do these cases, it will be asked, fit in with the neural theory of fibrositis? Yes, for the painful

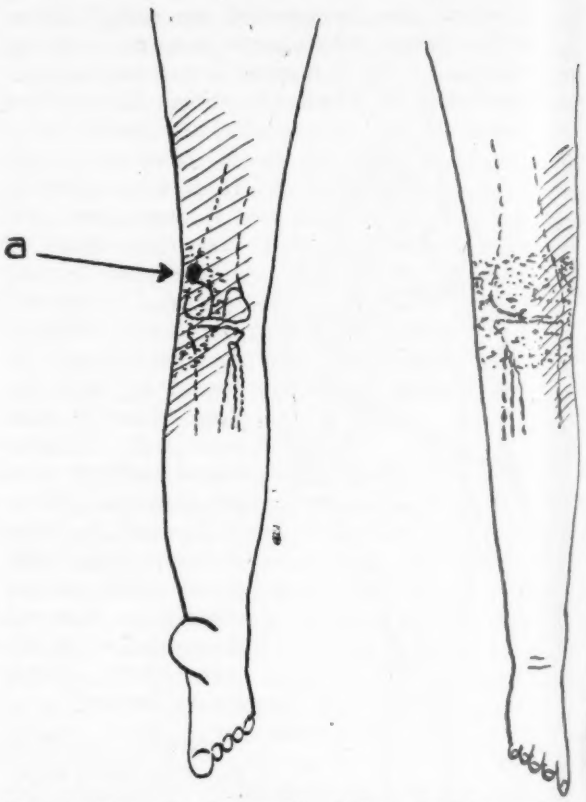

FIG. 6.—Case 4. A=myalgic lesion. Stipple=periarticular swelling. Hatching=deep tenderness which disappeared upon the injection of procaine into A.

sequelae of infectious diseases amount only to a persistence of the bodily pains which normally accompany influenza and other fevers. And all the general signs and symptoms of infection (fever, sweating, twitching, headache, stupor, etc.) are the result of the action of the toxin upon the central nervous system. The somatic pains, it must, therefore, be agreed, also proceed from a disturbance of the nervous system. It may be suggested, on the other hand, that the toxin gives rise to the pains by affecting directly the tissues of the body. This, I think, is the generally accepted view; but there is no reason why scattered bodily pains should not be regarded as a neurological symptom rather than a somatic one. With the strictly anatomical view usually taken of the nervous system, pains are seldom regarded as symptomatic of nervous disease unless they are confined to the fields of particular nerve trunks or dermatomes; for vague and wandering pains local causes only are sought.

The more recent views upon the deep pain system and its reflex activities have provided a basis upon which bodily pains can take their place as symptoms of nervous disorders. Pain anywhere in the body may be the result of abnormal reflex activity in the deep pain system, transmitted antidromically to the periphery. We have no positive evidence that bacterial toxins can directly affect the muscles in such a way as to cause pain, while we know that the nervous system is the intermediary in the genesis of all the remaining manifestations of fever. The painful lesions which accompany fever, therefore,

must result from enhanced activity in the deep pain system; and their spread and their persistence as fibrositic lesions (potential or actual) also must proceed from increased reflex activity in the neuronal pool (see Fig. 5). The increase of excitation in the pool of neurones causes changes in the tissues with which these neurones have functional connexion. And these tissues influence other tissues, and their persistence tends to increase the excitation in the cord; and so on.

Psychosomatic Rheumatism

Poynton (1936) suggested that a great advance in medicine would be announced if it could be proven that rheumatoid arthritis was a disease of the central nervous system. Rheumatoid arthritis, it is well known, sometimes follows nervous stress due to grief, anxiety, or exhaustion. Poynton and Schlesinger (1937) and Hubble (1943) have contended that in many cases of juvenile rheumatism, apart from chorea, there is evidence of a direct effect on the central nervous system. Hubble is not enamoured of the vague fashion in which many writers allude to the functional nervous aspect of some diseases; "to write and talk of 'psychosomatic' disorders", he said, "is to assume a bridge whose existence we but dimly discern and of whose nature we are ignorant". In a previous paper (Kelly, 1944*b*) the present writer has attempted to provide such a bridge between so-called "psychogenic" fibrositis and the nervous upset which might have had a share in precipitating it. If it seems certain that mental depression or nervous exhaustion has been responsible for fibrositic pains, it is not necessary to assume that the pains are hysterical or imagined. Many instances have been recorded in which profound rheumatic disease followed organic disease of the central nervous system; and it is equally easy to believe that minor rheumatic pains could be precipitated by a more transient disorder of the nervous system.

When the nervous system is deranged through anxiety or exhaustion, it is likely that its reflex activity may be enhanced so that baneful influences, which otherwise would have been ineffective, may be brought to bear upon the somatic tissues and give rise to fibrositic pain (see Fig. 5). The nervous disorder which precedes rheumatism, in fact, acts as a precipitating cause in the same way as an injury acts as a precipitating cause; i.e. by increasing the reflex activity of the centres responsible for the propagation of the disorder.

The Relation of Fibrositis to Rheumatism in General

The present fashion of dividing up the rheumatic group into distinct "disease entities" is a bar to progress in knowledge. Thus we often read of the need for accurate diagnosis of rheumatic diseases; but to me too great an insistence upon diagnosis and classification savours of putting the cart before the horse. Little indeed is known about the causes of rheumatism, or about the underlying pathological processes upon which the tissue reactions rest; yet we are asked to accept the necessity for a rigid classification of this vast amorphous group into a series of "entities" which cannot but be artificial. The layman's conception of rheumatism rests upon a broad anatomical basis, and medical science deceives itself if it imagines that it is able as yet to provide any more refined standards. The most diverse types of somatic ills, from sciatica and olecranon bursitis to rheumatoid arthritis, are called rheumatic, and we know there must be some relationship between them because we may see them occurring simultaneously in the same patient. The discovery of a key or common denominator will do a great deal towards converting chaos into order; and it is suggested that this key is provided by the fibrositic lesion.

Fibrositis has been portrayed here as a pathological rather than as a nosological concept; as a special kind of reaction in mesoblastic tissue, brought on by a number of different causes (known and unknown), rather than as a distinct "disease entity". In the early and transient cases, the pain may not be accompanied by any structural change in the tissues. In more advanced cases, changes recognizable as those of rheumatic disease occur. Acute lesions are characterized by a fibrositic reaction (or multiplication of connective-tissue cells with reversion to an embryonic type) accompanied by oedema. In the chronic cases this reaction becomes overshadowed by the process of repair, the formation of new fibrous tissue.

The fibrositic lesion, said Stockman (1904, 1911), is the basic unit of rheumatic disease. The fibrositic reaction, he said, may occur in any mesoblastic tissue; it produces special effects in the joints only because of the more differentiated tissues which are involved. Poynton and Schlesinger (1937) observed that soft tissue lesions occurred in all cases of rheumatic fever and rheumatoid arthritis. It is well known, too, that even advanced osteo-arthritic changes may be painless; the occurrence of pain often depends on the presence of muscular lesions. Arthritis represents only the effects of fibrositis upon the structures of a joint. But joints appear to possess a special affinity for the rheumatic process; and the reasons are clear:

1. *The Radiation of Pain.*—Kellgren (1938) commented frequently upon the curious fact that the pain from artificial deep lesions in the limbs tends to radiate to the joints. This is supported by clinical experience, which readily recalls the occurrence of unexplained "arthralgias" in febrile diseases, serum sickness, caisson disease, etc. The present writer frequently has observed the pain and tenderness of a joint to vanish upon the injection of procaine into a myalgic lesion.

2. *The Concentration of Mesoblastic Structures.*—All the structures of a joint are mesoblastic in origin. (*a*) The joint capsules, periosteum, and tendinous attachments are composed of adult fibrous tissue. (*b*) In the synovial membrane the cells are more rounded and more numerous, and

have assumed a secretory function. When disturbed they will proliferate freely and secrete an excess of fluid. (*c*) Cartilage cells also are fibroblasts which have differentiated. At the junction of cartilage with synovial membrane, intermediate types develop and the cartilage cells shade off almost imperceptibly into synovial cells (Maximow and Bloom, 1934). (*d*) Bone cells are connective cells with special qualities. In inflammatory states they may tend to "revert to type", and decalcification results.

3. *Vascular and Nervous Supply*.—The synovial membrane is freely supplied with blood vessels and nerves (Gardner, 1942, 1944). The vascular tissues, being mesoblastic, share the common affinity for the rheumatic agent. Fine nerve fibres (probably the pain-plexus) ramify freely both in the adventitious coats of the vessels and in the synovial membrane itself.

4. *Movement*.—The synovial and supporting structures of a joint are subject to a much greater degree of mechanical strain than are the fascial and intermuscular planes. When a joint becomes involved in an acute rheumatic process, its recovery depends to a large extent upon the amount of rest that can be secured. The secretory function of the synovial cells becomes exaggerated, and further damage is caused by movement. Thus a vicious circle comes into operation, which can be broken only by assuring rest to the joint. The inflamed and proliferating cells become further deranged if subjected to mechanical strain.

The manifestations of arthritis, if the reflex hypothesis is true, represent trophic nervous effects. Proliferative and degenerative changes take place side by side, conditioned by abnormal nervous stimuli which cause the normal functions of the tissues to become deranged.

Neuropathic Joints

Charcot's joint is a familiar example of the effect of deranged nervous influences upon mesenchymal tissue. The destructive and explosive changes are but an exaggeration of the effects seen in other forms of arthritis (King, 1930; Knaggs, 1932); and their special character is due to the abnormal nervous supply to the tissues. Once the Charcot joint was regarded as a thing apart—a special form of arthritis with no relation to the milder and multiple forms seen in osteo-arthritis and rheumatoid arthritis. In reality, however, it represents but the most advanced stage of arthritis, in which the effects of abnormal neural influences are most apparent. The neuropathic joint is the exception which proves the rule; it exemplifies and emphasizes the important part played by nerve impulses in the larger group of rheumatic disorders.

An Earlier Neural Theory of Rheumatic Disease

A nervous theory of rheumatism which flourished last century had its origin 100 years previously in the "vitalistic" hypothesis of disease embraced by Stahl and Hoffmann, and by William Cullen of Edinburgh. Professor J. K. Mitchell (1831), the father of the more illustrious Weir Mitchell, wrote of the spinal cord as the seat of rheumatism, which he held to be a manifestation of the disordered activity of nervous tissue. Paget came to give strong support to the theory; and both Weir Mitchell (1872) and Charcot (1877) contended that the trophic nerves to the joints were responsible for the manifestations of arthritis. This view was adopted by the majority of the leading physicians of the latter half of last century, including the Edinburgh teachers Laycock (1864) and Liveing (1873), and Ord (1880) Duckworth (1880) and Latham (1886) of London, and many others. The theory was sent into oblivion by the triumphant onrush of bacteriology, assisted by the sledgehammer blows of Maclagan (1896), who held it up to scorn. Bacteriology, however, has failed to solve the problem of the nature of rheumatic disease. During the past few years more attention has been given to the part played by the nervous supply in the nutrition of tissues. Plewes (1940) and L. C. Kelly (1943) have given good reasons for regarding osteo-arthritis of the hip as a trophic disorder, while Kelikian (1943) contends that neural influences are responsible in many other instances of chronic arthritis. Pemberton and Scull (1943) and Stone (1943) regard the polyarthritic syndromes as manifestations of underlying central disorders.

The important part played by nervous influences in ensuring the orderly functioning of tissues, so clearly obvious to the clinicians of last century, is almost forgotten to-day. There seems to be a mystic quality about such a view that records ill with our present fashions, which prefer to seek for bacteriological, biochemical, or mechanical causes for our ills. Many, indeed, are forgetful of the unseen neural control which co-ordinates all the activities of living tissues. When separated from nervous control, muscles fibrillate and waste away, squamous epithelium becomes thin and shiny, subcutaneous tissues atrophy, and fat loses its structure. The delicately integrated mechanisms of the nervous system keep watch over every part of the body, so that each tissue preserves its normal function and its normal structure. In rheumatism, influences from within or form without have disturbed that balance, and the loss of integration is reflected in dystrophy of the tissues.

Summary

1. According to the neural theory of fibrositis, the mechanism by means of which a myalgic lesion follows an injury is the same as that by which painful spots appear in the body wall during visceral disease.

2. The process is dependent upon an increase of reflex excitation in the deep pain system.

3. The formation of multiple lesions after injury is dependent upon a spread of this excitation in the cord.

4. A like explanation holds good for the multiple

rheumatic lesions which follow a febrile illness (e.g. rheumatic fever); and for so-called " psychogenic " rheumatism.

5. The fibrositic lesion is the basic unit of rheumatic disease, which presents characteristic appearances in joints only because of the special qualities of the articular structures.

6. Reference is made to the fact that the clinical teachers of last century generally took the view that rheumatism was a disorder of the central nervous system.

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EPILOGUE TO THE SERIES ENTITLED "THE NATURE OF FIBROSITIS"

BY

MICHAEL KELLY

No claim is made that a new hypothesis has been propounded, for a neural theory of rheumatism is two hundred years old. The present observations represent merely the collected observations of many others, perhaps co-ordinated a little and brought up to date with modern neurophysiology. Plenty of corroborative evidence is to hand in the literature, did one but take the trouble to collect it.

No claim is made, either, that the " cause " of rheumatism has been discovered; rather is it suggested that the mechanism has been traced through which the various causes bring about their end-results. There is no single cause for this group of diseases; more likely it is the result of a number of causes, which in different cases may be different, though perhaps acting through the same mechanism. To the casual glance a stiff neck does not resemble rheumatoid arthritis; but neither does a furuncle resemble chronic osteomyelitis, and in the days before Lister it would not have been easy to believe that they were due to the same cause. By agreeing to speak of " rheumatism ", we all display our belief in the basic unity of rheumatic disease; but, with no clear view of its essential nature, we are forced to divide it up into a number of separate " entities ", which may prove to be as closely linked to each other as the various staphylococcal infections are linked to each other.

The proposed theory, it is feared, has not dramatic appeal enough to shake the old-established beliefs even in their present confused state. It demands a retracing of the steps over some sixty years, and the discarding of much that we have been taught to accept as self-evident. Even supposing it to be true, many may wonder if it is useful, because it opens up no royal road to the prevention or the cure of rheumatic disease. The answer, of course, is that the truth should be sought at all costs, for itself alone. If the theory is proven to be erroneous, no harm will have been done, for it has been well said that truth is more likely to emerge from error than from confusion.

It has been wisely stated, also, that the value of hypothesis lies not so much in the ingenuity of invention as in the labour of verification. The verification of this hypothesis depends upon the painstaking and careful observation of mild and transient cases of somatic pain, and of early cases of rheumatic disease. Rheumatism clinics rarely see such common affections as the transient spreading pains which sometimes follow mild injuries or infections; and these, perhaps, could throw a good deal of light upon the mechanism of the rheumatic process. They usually remain in the hands of the general practitioner; there can be little doubt, therefore, that the observant general practitioner holds the key to the situation.

THE INCIDENCE OF RHEUMATISM

BY

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In the Report of the Medical Advisory Committee (Scotland) on the Chronic Rheumatic Diseases, the fact is stressed that "there are no means at present of assessing the amount of rheumatism among the non-insured population or in non-incapacitated insured persons".

In an attempt to provide figures relating to a whole population (though a small one) an inquiry was devised to ascertain the amount of rheumatism medically treated in the Burgh of Kilmarnock and the immediate surrounding district—population 40,000 (estimated)—during the month of November, 1945.

Method

Every general practitioner in the Burgh was approached and the scheme outlined to them. Each agreed to furnish information daily, on a specially designed card, of all his items of service, and of all services in respect of rheumatic conditions. Spaces on the card were reserved for noting rheumatic cases seen for the first time during the month, and also for noting the type of rheumatism. The card was also divided for sex and age, there being three age groups for each sex: under 15 years, i.e. children; 15 to 65 years, i.e. persons of working age; and over 65 years, i.e. mainly retired persons. The cards were taken to the doctors' surgeries daily, and when the cards for the day of call were left the completed cards for the previous day were collected and brought to the Public Health Department. The information from the cards was abstracted daily, and if there was any doubt about the meaning of an entry personal contact was made with the practitioner so as to be sure that no wrong interpretation took place.

The classification of rheumatism adopted was that suggested in the Report of the Medical Advisory Committee, as follows:

Acute group	*Articular group*	*Non-articular group*
(*a*) Rheumatic fever	(*a*) Rheumatoid type	(*a*) Muscular type
(*b*) Subacute rheumatism	(*b*) Osteo-arthritic type	(*b*) Neuritic type

The findings are set forth in Tables 1 and 2.

TABLE 1

SHOWING ALL ITEMS OF SERVICE AND THOSE IN RESPECT OF RHEUMATIC DISEASES—NOVEMBER, 1945

	Males			Females			Total
	Under 15	15–65 yrs.	Over 65	Under 15	15–65 yrs.	Over 65	
All items of service, i.e., visits and consultations	1,296	5,754	508	1,371	7,902	809	17,640
Items, i.e., visits and consultations, in respect of rheumatic conditions	21	528	21	25	591	42	1,228

TABLE 2

SHOWING CASES SEEN FOR THE FIRST TIME DURING NOVEMBER, 1945, REFERRED TO AS NEW CASES, ARRANGED ACCORDING TO THE CLASSIFICATION SUGGESTED BY THE MEDICAL ADVISORY COMMITTEE

Population at risk	Males			Females			Total
	Under 15	15–65 yrs.	Over 65	Under 15	15–65 yrs.	Over 65	
	5,276	12,000	1,790	5,295	13,524	2,115	40,000
Acute rheumatism	—	3	—	1	3	—	7
Subacute rheumatism	2	14	1	2	17	1	37
Articular: Rheumatoid arthritis	—	23	1	—	29	6	59
Osteo-arthritis	—	7	7	—	13	5	32
Non-articular: Muscular rheumatism	5	154	6	3	131	10	309
Neuritic rheumatism	—	53	4	1	56	7	121
Total new cases.. ..	7	254	19	7	249	29	565

An effort was made to repeat the investigation during the month of March, 1946, but unfortunately on this occasion the doctors in one partnership were unable to take part in the inquiry. From the information gained in November the new population at risk was, therefore, estimated at approximately 30,000. The figures for the second part of the investigation are shown in Tables 3 and 4.

TABLE 3

SHOWING ALL ITEMS OF MEDICAL SERVICE AND THOSE IN RESPECT OF RHEUMATIC DISEASES—MARCH, 1946

	Males			Females			Total
	Under 15	15–65 yrs.	Over 65	Under 15	15–65 yrs.	Over 65	
All items of service, i.e., visits and consultations	1,429	4,786	596	1,474	5,964	953	15,202
Items, i.e., visits and consultations, in respect of rheumatic conditions	24	367	28	22	356	68	865

Table 5 shows the parts first affected in articular cases in both months. Table 6 shows the part first affected in non-articular cases, and again relates to both months.

TABLE 4
SHOWING CASES SEEN FOR THE FIRST TIME DURING MARCH, 1946, ARRANGED ACCORDING TO THE CLASSIFICATION SUGGESTED BY THE MEDICAL ADVISORY COMMITTEE

Population at risk	Males			Females			Total
	Under 15	15–65 yrs.	Over 65	Under 15	15–65 yrs.	Over 65	
	3,960	9,000	1,342	3,975	10,140	1,583	30,000
Acute rheumatism	4	3	—	3	1	—	11
Subacute rheumatism	6	8	1	4	15	3	37
Articular:							
Rheumatoid arthritis	—	14	3	1	17	6	41
Osteo-arthritis	—	13	8	1	12	5	39
Non-articular:							
Muscular rheumatism	2	120	5	1	103	17	248
Neuritic rheumatism	—	41	4	—	32	9	86
Total new cases	12	199	21	10	180	40	462

TABLE 5
PARTS FIRST AFFECTED IN ARTICULAR CASES—NOVEMBER, 1945, AND MARCH, 1946

	Spine	Shoulder	Elbow	Wrist	Fingers	Hip	Knee	Ankle	Feet	Others	Total
Acute rheumatism	—	1	3	2	—	—	6	5	—	1	18
Subacute rheumatism	—	6	6	8	—	6	17	17	4	10	74
Rheumatoid arthritis	3	2	2	14	22	3	35	11	5	3	100
Osteo-arthritis	11	5	—	3	4	18	24	3	2	1	71
Total	14	14	11	27	26	27	82	36	11	15	263

TABLE 6
PARTS FIRST AFFECTED IN NON-ARTICULAR CASES—NOVEMBER, 1945, AND MARCH, 1946

Muscular rheumatism

Neck	Shoulders	Arm	'Lumbago'	Lower limb	Chest wall	Others	Total
73	75	5	333	37	7	27	557

Neuritic rheumatism

Occipital neuritis	Brachial neuritis	Neuritis of forearm	Intercostal neuritis	Sciatica	Neuritis of leg	Others	Total
8	55	2	25	102	6	9	207

Discussion

Cards were returned by each practitioner for each day he practised during the month of November, 1945; and similarly, with the exception of the partnership which did not participate, cards were returned each day in March, 1946.

The month of November, 1945, was an exceptional one from the meteorological point of view. There was only 0·39 inch of rainfall, and rain fell during 5½ hours only. It was the driest November on record, i.e., for almost 100 years. March, 1946, on the other hand, showed weather of two distinct types. At the beginning of the month there was a cold spell with temperature below the normal, while from March 17 onwards, the temperature was above normal. There were 2·73 inches of rainfall—just above the average. The following figures indicate the difference in the meteorological conditions:

	November, 1945	*March*, 1946
Rainfall (in inches) .	0·39	2·73
Average relative humidity (percentage) .	90·2	80·9
Sunshine (number of hours)	38	101
Average day shade temperature . .	50·8°	49·6°
Prevailing wind . .	East	First fortnight, east Second fortnight, west

A perusal of the figures in Tables 1 and 3 shows that all items of service, i.e., visits and consultations, were relatively more frequent in the second period—amounting to 44 items per hundred of the population in November, as compared with 51 items per hundred of the population in March. During March there was a considerable amount of measles, whooping-cough, and catarrhal conditions, which may account for some, at any rate, of the increased proportion. Considering the items in respect of the rheumatic conditions, the picture is different. In November there were just over 3 items of service per hundred of the population, and in March there were just under 3 items of service per hundred of the population. The difference in the numbers is very slight although the weather in the two months was quite dissimilar. There was proportionately slightly more acute rheumatism and subacute rheumatism and also osteo-arthritis in March than in November, but the other items—the rheumatoid and the non-articular group—were almost equal in incidence in the two months.

Rheumatic conditions accounted for 6·98% of all medical attendances during the month of November, 1945, and for 5·69% of all medical attendances during the month of March, 1946. These percentages are less than the figure found by Davidson and Duthie (quoted in the Report of the Medical Advisory Committee) viz., 9·4% of all attendances during an average winter month in 1937 in Aberdeenshire.

Tables 2 and 4 set forth the detailed numbers of rheumatic conditions encountered. It should be clearly understood that in these tables the term "new case" is used in a special sense. The case might in effect be either a new case in the ordinary sense, or a patient suffering from a recurrence of a rheumatic condition and who was attending or being attended for the first time during the month, or a patient already suffering from a rheumatic condition and who was receiving from or paying to his doctor his first visit during the month in question. The figures, then, must not be taken as indicating the true incidence of new cases of rheumatic infection, but rather as indicating the incidence of the different

types of the rheumatic diseases. Judging from the tables, rheumatism in the young appears to be a very uncommon event in comparison with rheumatism in other age groups. In the working age groups there were significantly greater numbers of rheumatic conditions recorded than in the other groups. (The χ^2 test gives $P<0{\cdot}01$.) The question of certificates of incapacity for employment may have to be considered in assessing the reasons for the increased incidence at working ages, but this increase occurred in both sexes. There was a less marked emphasis on the female sex, but the difference was still a significant one. The amount of rheumatism in older people is relatively less than at the working age groups. One might reasonably have expected to find an increase in the incidence with increased age. It is possible that by the time a person has reached the age of 65 years he or she may regard some rheumatic conditions as a matter of course, and may, therefore, not seek medical advice so frequently for them. It is almost certain that a much greater proportion of those entitled to free medical service would be seen by doctors than those who had to pay private fees—especially for the less severe types of disease—and in this respect the figures would be unduly loaded with insured persons.

The incidence of acute rheumatism was not great and most of it was met with in the 15–65 years age group.

By " subacute rheumatism " is to be understood a subacute form of rheumatic fever and not an acute form of rheumatoid arthritis. Here the incidence was fairly evenly divided according to age groups, with again a higher incidence at the ages of active work. It should be noted that the incidence of acute and subacute rheumatism in the under 15 age group was higher in March, 1946, than in November, 1945.

Rheumatoid arthritis was only once recorded in a child. A point of interest is the high proportion of cases of rheumatoid arthritis in males in both months. Whereas the proportion of males to females has often been quoted as low as 1 to 3, in this series of cases it is approximately 2 to 3. Rheumatoid arthritis was more frequently encountered than osteo-arthritis. This again is at variance with the findings of Davidson and Duthie (Medical Advisory Committee Report), who reported the proportion of rheumatoid cases to osteo-arthritic cases as 5 to 8. In this series, the proportion was approximately 10 to 7. Osteo-arthritis was only once recorded in the youngest age group and appeared almost equally often in both sexes.

In the non-articular groups the disease is almost unrecorded in children and surprisingly little recorded in the older age groups. Here the incidence is heavy at the working ages, and the excess of males in the muscular groups is made up almost entirely of cases of lumbago. The neuritic cases showed no marked preference for one sex.

Table 5 sets out the parts first affected in the articular cases. The most outstanding finding was the high incidence of cases showing the first affection in the knee joint. There was no marked difference in the side affected: symptoms began almost equally often in the right, in the left, or in both knees together. It is surprising to find the knee first affected so frequently in all categories, and to find it first affected more than twice as commonly as any other joint. The reason for this high incidence is not clear, but it may be concerned partly at least with the high incidence of males in the rheumatoid group, there being 18 such cases out of the 41 males, and only 17 out of the 59 females.

Table 6 shows that by far the commonest site for muscular rheumatism was the back, and that the only other common sites for this condition were the neck and shoulders. Sciatica took first place in the neuritic group, and in this group the only other condition at all frequently noted was brachial neuritis.

Tables 2 and 4 show that approximately 9% of the cases recorded were of acute and subacute rheumatism; 17% were chronic articular cases; 54% were cases of muscular rheumatism; and 20% were of neuritic rheumatism.

Summary

1. The complete figures for medical attendances in general practice are recorded for the Burgh of Kilmarnock and the immediately surrounding district for the month of November, 1945.

2. Similar figures for approximately three-quarters of the population of the Burgh of Kilmarnock are recorded for the month of March, 1946.

3. The items of service in respect of rheumatic conditions are separately stated.

4. Rheumatic conditions accounted for 6·98% of all medical attendances during November, 1945, and for 5·69% of all medical attendances during March, 1946.

5. Details of the rheumatic conditions encountered are recorded.

I wish to thank Professor L. S. P. Davidson, Professor of Medicine, University of Edinburgh, for much helpful advice and criticism; Dr. R. A. Robb of the Mathematics Department, University of Glasgow, for advice on statistics; and Mr. William Dunbar for information regarding the weather in Kilmarnock during the months of November, 1945, and March, 1946. I wish also to record the names of the general practitioners without whose willing help the data would not have been available. They are: Drs. J. G. Allardice (November investigation only), J. Cochran, G. M. Currie, W. D. Frew, R. C. Hamilton, J. McAlister, I. B. K. MacGregor, (March investigation only), P. M. McKillop, W. B. G. Mair, J. W. Peden, A. Robertson, A. C. Scott (November investigation only), and J. Shanks.

REVIEW OF GOUT, 1939–1946

BY

L. C. HILL

The main contributions to the subject of gout during the period under review have not unnaturally come from American workers. In spite of outstanding research by Talbott and Coombs (1938), Bauer and Klemperer (1942), and others into the metabolic and clinical aspects of the disease, the essential problem remains unsolved. Gout used not to be regarded very seriously by American physicians, and it is only during the last decade that it has been recognized as a not infrequent cause of arthritis.

Incidence

Hench's claim (1935) that patients with gouty arthritis constitute at least 5% of all patients seen at the Mayo Clinic suffering from joint disease was supported by Kahlmeter (1938), by Kinell and Haden (1940) in their review of 62 cases of gout, and recently by Wright (1945) in Canada. Experience of work in two rheumatic hospitals in this country leaves an impression that this proportion is certainly not too high, especially considering the number of cases of acute gout which never reach hospital but are treated privately, and also the atypical forms which, even with long experience and the full resources of the laboratory and *x*-ray department, are difficult to recognize. Whatever be the incidence, sufficient evidence is now available to prove that gout is not a rare disease, and if it is diagnosed less frequently in this country and in Europe nowadays than heretofore, this merely reflects more accurate diagnostic criteria.

Heredity

Recent work has strengthened the impression that gout is a hereditary disease, and has confirmed the statement of Futcher (1914) that a woman can transmit the diathesis to her offspring without herself developing the disease. The medico-sociological studies of Talbott and of Coombs (1938 and 1940) are very interesting. An exhaustive examination was made of 136 blood relatives of 27 patients with well established gout, none of whom had ever had an attack. A plasma uric acid of over 6 mg. per 100 c.cm. was found in 25%, and of this number 80% were males. No alternative cause, renal or otherwise, could be found to account for the findings. These workers, therefore, conclude that the gouty constitution is a hereditary predisposition based on hyper-uricaemia, and they relegate social factors, environmental influences, and dietetic indiscretions to a position of secondary importance. A life-long follow-up would be necessary before it can be known what proportion of such affected relatives will later develop clinical gout. It is difficult to see much justification for Talbott's hypothesis (1946) that such hyper-uricaemia is due to increased production of uric acid in the body, but this point will be discussed later. Smyth and Freyberg (1942), in their study of the hereditary nature of gout, have approached the problem from the same direction, with similar results save that in their investigations they found no single female relative with a raised blood uric acid. In a big series, Bauer (1943) found a family history in 75% of patients. An additional allergic factor in the family history was claimed by Burt and Gordon (1939), and also by Mackay (1939) in some cases, but unfortunately no figures are quoted. This attractive hypothesis would account for the undoubted sensitiveness of many gouty patients to certain articles of diet and alcoholic beverages, an aspect which is much too lightly dismissed by the American workers.

Metabolism

The great majority of modern workers agree in classing gout as a metabolic disorder, though no clear evidence of any disturbance of the metabolism of purines and nucleo-proteins has been produced. There will be general agreement with Talbott (1946) that the term " urate " should replace " uric acid ", since, in the serum and body fluids, 97% of uric acid is in the form of sodium urate. The terms " uric acid " and " urate " are used synonymously throughout this review.

No new facts are available from a study of the literature of the period to explain satisfactorily the main problems in gout—namely, the altered excretion of urate, the raised blood uric acid, and the deposition of urate in the tissues.

Blood Uric Acid.—Considerable difference of opinion exists with regard to the blood uric acid level in gout. In 900 tests on 100 patients with gout (in all stages of the disease), 98% were found by Talbott (1946) to have 6 mg. per 100 c.cm. or more in the serum, the average being 8·8 per 100 c.cm. This compared with the normal finding (less than 6 mg. per 100 c.cm.) in 96% of 400 non-gouty control tests. These are surprisingly high figures and do not accord with day-to-day experience, though the figure of 90% was quoted by the writer in a study of 93 cases of gout (Hill, 1938). Comparable figures are not readily available, but Bauer states that the blood uric acid levels are always inconstant and irregular. Coombs (1940), and Bauer and Klemperer (1942) support the thesis that the serum urate in gouty patients is above normal, in contrast to the

constantly normal findings in all other arthritic conditions and most other morbid states. A further group of patients collected by Cohen of Philadelphia, and quoted by Talbott (1946) in his book on gout (p. 95), showed a level of 6 mg. per 100 c.cm. or over in all but 3 of 36 cases of clinical gout, and even these 3 had had at other times concentrations greater than 6 mg. per 100 c.cm. The failure of some physicians to have faith in a raised uric acid may be attributed, according to Talbott, to the selection of whole blood in preference to serum or plasma. This is stated to be less reliable because of the concentration of interfering substances in the red cells, which act in some cases by modifying colour development.

In the writer's personal experience values below 6 mg. per 100 c.cm. have from time to time been found in patients suffering from established gout, particularly during an acute attack, and this phenomenon was mentioned by Waterhouse (1938), whose long clinical and pathological experience of the subject merits attention The reasons for these discrepancies remain obscure. Kinell and Haden (1940) advise that too much dependence should not be placed on a raised blood uric acid, especially in the early stages. Cecil (1941) states that many patients with gout do not show a raised uric acid, especially in the acute stages of the disease.

Purine Metabolism.—Urate is the end-product of purine metabolism, and that excreted in the urine derives from both endogenous and exogenous sources. Research work by Bauer, Talbott, and others has confirmed Pommer's (1933) original figure of 300 mg. of urate excreted daily on a purine-free diet of adequate calorific value. This represents the endogenous portion. The exogenous urate is derived from foods with a high purine or nucleo-protein content, but as Wright (1945) states " to regard this as the underlying cause of gout is akin to asserting that carbohydrates are the cause of diabetes ".

There is no conclusive evidence to support any of the three possible metabolic dysfunctions which might conceivably lead to increased concentration of urate in the blood or serum; i.e. (1) diminished destruction of urate by the body; (2) diminished excretion by the kidney; (3) increased formation by the body. Destruction of either endogenous or exogenous uric acid has never been proved in human beings, and no enzyme has ever been discovered in the body capable of initiating such destruction. Altered excretion of urate by the kidneys is the popular current explanation and is supported by, among others, Bauer (1943), Thannhauser (1929), and most modern writers on the subject; but the work of Coombs and his associates (1940) and of Talbott (1946) brings experimental evidence to show that there is no differential inability of the kidneys in gout to clear urate. These workers state that little difference exists between gouty and non-gouty persons in regard to renal exchange of urate, and that when urate reabsorption is interfered with by the action of such substances as atophan and salicylate, gouty and non-gouty persons respond in a similar manner. It is only when unmistakable signs of renal impairment are found that urate clearance is affected through a critical depression in glomerular filtration rate. Wright (1945) of Canada supports these views.

On the basis of a persistent increase in the total daily excretion of urate demonstrated in a group of gouty patients and also in non-affected relatives of gouty patients, Talbott (1946) believes an increased formation of urate to be the fundamental metabolic factor; but his arguments are not entirely convincing and he appears to arrive at this conclusion more by the process of elimination than by factual evidence. The occasional occurrence of gouty arthritis in patients with leukaemia and polycythaemia vera (Reifenstein, 1939; and Tinney and his co-workers, 1945), diseases which are known to be associated with hyper-uricaemia due to endogenous nuclear katabolism, is adduced as evidence to support this. The numbers are, however, very small: in one series, only 8 out of 168 patients with polycythaemia vera, over a period of several years, developed gout. Incidentally it was observed that the level of the blood uric acid was not proportional to the severity of the polycythaemia. It is to be noted that high uric acid levels are found in chronic nephritis, but the development of gout in such cases is extremely rare.

On the other hand Bauer and Klemperer (1942) postulate a selective deficiency in elimination not necessarily associated with demonstrable renal impairment.

Interesting work on the renal exchange of urate has been carried out by Smith (1937), and Smith and his associates (1938), and confirmed by Talbott (1946). They were able to measure the rate of formation and flow of glomerular filtrate and to note that the concentration of urate is similar to that found in plasma. Slightly more than 90% of the urate in the glomerular filtrate is reabsorbed by the tubules, as compared with over 98% of the fluid, with the result that the concentration of urate in bladder urine is several times greater. Urate clearance data in 28 gouty patients without obvious renal impairment showed no essential differences from those found in 55 non-gouty controls. Only when renal function is impaired to an extent capable of depressing glomerular filtration is retention of urate demonstrable. Recent work on the effect of drugs on urate clearance by Price (1945) and Coombs and his associates (1940) confirms earlier observations. Atophan and salyrgan appear to act by insulting the tubular epithelium, thus interfering with urate reabsorption, while salicylate diuresis is said to occur as a result of the preoccupation of tubular cellular activity in salicylate excretion to the detriment of urate reabsorption. Colchicine has no effect upon urate clearance. Its mode of action is entirely unknown.

Morbid Anatomy

In the period under review little if any fresh light has been thrown on the morbid anatomy of gout.

The one distinguishing feature remains the deposition of urate in the tissues, both soft and bony, and the inflammatory and degenerative change resulting therefrom. Talbott (1943) believes that such deposition precedes the acute attack and takes place from the synovial fluid without previous necrosis. The theory, held by many, that the acute attack of gouty arthritis is caused by the bursting into the joint space of a uratic deposit, remains to be proved. The loss of bone in the area of urate deposition is probably due to local inhibition of osteoblastic activity, so that when the bone is normally absorbed, it is not replaced. Most of the anatomical variations observed in the late stages of gout are probably the results of arteriosclerosis, which in its turn is secondary to renal impairment. The varied terminology given to the renal lesions of gout indicates the lack of unanimity of opinion concerning the exact nature of the change, but the great majority of workers now agree that such changes are the result and not the cause of gout.

The effects of gout upon the cardiovascular and renal systems have formed a basis for discussion and argument for many years, but opinion that there is no direct relationship is strengthening. Recent work by Steinberg (1945) found no statistical evidence connecting gout with either angina, hyperpiesia, or renal calculus, while Koller and Zollinger (1945), examining the kidneys of 5 cases of gout, found a sclerotic condition—involving glomeruli, arteries, and interstitial tissue—which they consider similar to the changes found in diabetes.

Clinical Aspect

Conventionally the first sign of gout is an acute attack in a joint, and the diagnosis is usually not suspected until the attack has occurred. Prodromal symptoms have been widely described and formed an important part of the description of the disease, particularly among late nineteenth-century writers. Such premonitory symptoms include depression, insomnia, nightmares, flatulence, constipation, dyspepsia, anorexia, nausea, vomiting, and polyuria. According to Wright (1945), the majority of patients have no such symptoms, while a small percentage undoubtedly do. Talbott (1946) agrees with Wright, and considers that while many persons have premonitions of an impending attack, the majority of such symptoms are to be attributed to precipitating factors and are not an integral part of the acute attack. No subsequent description of the acute attack has excelled in vividness and simplicity that of Thomas Sydenham in 1717, written from personal experience. There is general agreement that the onset is usually at night and that the pain is intense, being variously described as " vice-like ", as if " dipped in molten lead ", etc. The pain appears to be caused by a rapid effusion into the joint space, with oedema of the surrounding tissues. Tenderness is a typical feature, and is usually maximal over the lateral aspects of the involved joint. As compared with an acute suppurative arthritis, the skin tends to be tense, shiny, and cyanotic, rather than fiery red. Acute attacks usually involve joints, but very occasionally non-articular structures are attacked, notably a subcutaneous bursa or the helix of the ear, in which case pain is much less severe. The site of the first attack is usually the metatarsophalangeal joint of the great toe. Talbott agrees with Scudamore (1823) that this is so in 60% of all cases, while other workers, including Bauer (1943), put the figure at 50%. Treatment is the most important single factor in determining the duration of an attack. If adequate, it may abort a mild one and appreciably shorten the duration of a severe one. Prolongation of the acute phase may be caused in untreated cases by repeated small attacks, and this is more likely to occur in patients with advanced chronic gout. Most writers, including Cecil, Bauer, and Talbott, fix as a dividing-line between acute and chronic gout the stage when the joint fails to return to normal after an acute attack. There is also general agreement that the earlier the age at which the first attack occurs the more the likelihood that distribution will be polyarticular and that constitutional and chronic joint changes will develop. When gout develops over the age of fifty it is usually mild and the prognosis good.

Precipitating factors.—Indiscretions in eating and drinking have long been blamed for inciting acute attacks. Alcohol and purine-rich foods are particularly suspect, while certain specific foods have been claimed to produce acute attacks, supposedly by an allergic reaction. Talbott (1946) holds that " gout is an hereditary metabolic disease, relatively immune to incidental items such as food and drink. The presumption that particular foods are harmful to gouty patients is not an empiric observation. It is a prejudice ". Bauer (1943), writing in the same vein, regrets that such teachings are shrouded in the semi-sanctity of a long and venerable heritage, and have never been subjected to experiment or analysis. If it is agreed—and the evidence is all in favour of it—that gout is a hereditary disease, then obviously dietetic factors cannot be causative. The whole position remains obscure. Certain workers, including Bauer (1943), have found that most gouty patients do not react to occasional excess purine feeding, and they also note that acute attacks over a period have not coincided with a high purine intake. It is an established fact that gout occurs occasionally in vegetarians. Talbott (1946), while virtually denying that alcohol in any form influences the disease, admits that in some cases a high purine diet does appear to initiate attacks. Burt and Gordon (1939) stress the sensitiveness of gouty patients to certain articles of diet or certain products of metabolism, and regard the acute attack as an allergic manifestation. This view is strongly supported by Mackay (1939), who considers that the hereditary element in gout is twofold, consisting of a gouty diathesis (presumably associated with a tendency to high serum uric acid) and an allergic diathesis. This second factor is not invariably

present, but when it is it accounts for the sensitiveness to various items of food, etc. More universally accepted excitants of the acute attack include drugs, trauma, infections, and surgical operations. Attacks of gout have followed injections of liver (Herrick and Tyson, 1936; and Krafka, 1935), salyrgan, insulin, ergotamine tartrate, and vitamin B_1 (Vorhaus and Kramer, 1938). The mechanism by which they act is variously described, but the case reports are too few to do more than suggest an association. That trauma (in whatever form), and acute infections are precipitators has been recognized from early times. Recently Hench (1940) has drawn particular attention to the significance of postoperative gout.

Complications

Renal disease.—Renal disease is the most serious complication. In a series of 77 autopsies on gout, Gudzent (1928) found only 4 showing no sign of renal disease. Bauer states that the majority of gouty patients die from uraemia. This has not been the writer's experience in practice, though it is probably true of those who die below the age of fifty-five. There will be general agreement with Hench's dictum (1940) that any chronic arthritis associated with renal disease is almost certainly gout. In two series of cases published by Talbott (1943), approximately 50% of patients showed an impairment of one or more renal functions, and Talbott believes that if additional tests had been performed the figures would have been still higher. He concludes that the majority of patients with gout, irrespective of age or duration of symptoms, have some impairment of renal functions. Coombs and his co-workers (1940) demonstrated some degree of renal impairment in a still higher percentage of patients with gout. They find that the most constant feature is the inability to concentrate solids maximally, and state that neither age nor duration of symptoms, nor the level of uric acid concentration, is the sole determining cause. They conclude that renal changes are always the result and never the cause of gout. On the other hand, Burt and Gordon (1939) maintain that chronic nephritis is not a common sequela of gout.

Vascular disease.—Arteriosclerosis and hypertension are stated by Talbott to occur more frequently in young gouty patients than in those in a similar age group suffering from other chronic diseases. In Talbott's series no instance of malignant hypertension was seen, all cases being of the benign type. He argues against any close association between hypertension and renal disease in gout. Coombs and his associates, and Bauer, on the other hand, found that in their series of patients with renal impairment over 40% either had or later developed benign hypertension. In their opinion this hypertension is arteriosclerotic in type and is secondary to prolonged renal damage and reduced renal flow. They state that when it occurs in gout it is a late manifestation. Steinberg (1945) found no evidence to support a connexion between gout and angina or hyperpiesia.

Urinary Calculi.—According to Hench, writing in 1940 (and quoted by Bauer in 1943) urinary calculi are relatively common in gouty patients: he found them in 12% of his series. Talbott (1943) mentions 4 patients in whom renal colic was the presenting symptom, preceding the first acute attack by a year or more. He considers it a rare complication. It is reasonable to agree with Bauer (1943) that when an arthritis is associated with urinary stone it is probably gout. At one time or another virtually every part of the body has been stated to be involved in the ravages of gout, but often the evidence is extremely slight. Talbott is reluctant to call any complication gouty unless it is associated with urate deposition or has a high incidence in gouty patients. Gundeson (quoted by Talbott, 1946), in a series of 30 consecutive cases, was unable to observe by slit lamp any traces of urate crystals in the lens, and so he could not confirm Weve's original findings (1924). In a much larger series Talbott found no disproportionate occurrence of skin lesions, psoriasis, or eczema. He did note, however, that those who had these conditions reported that they tended to flare up during acute attacks. Bauer agrees with this, and considers that all these conditions are probably unrelated to gout.

Associated Diseases

The association of gout with lead poisoning has been stressed for a generation or more, particularly in England and in Germany, where in a big series of cases of lead poisoning Strierlin (1932) found 3% to be suffering from gout. The association appears to be rare in the U.S.A., Talbott (1946) finding only one case of lead poisoning in his large series. There is no ready explanation for the discrepancy between European and American data. In the writer's opinion the frequency of the association has been over-stated in this country, and he found no single case of lead intoxication in his series of 93 cases. In fairness to the older British physicians it must be admitted that the association is naturally more infrequent to-day, since lead poisoning is now rare. This is discussed in Allbutt's *System of Medicine* (1897), and also by Allbutt and Rolleston (1907). There will be little tendency to disagree with Talbott or Bauer when they deny any connexion between gout and diabetes, but few will associate themselves with Talbott when he states that the majority of his gouty patients are not obese. Kinell and Haden (1940) in their review of 62 cases, take the traditional view when they state that gout appears typically in obese, healthy-looking middle-aged men engaged in sedentary occupations, and Wright (1945) agrees with them.

It is generally admitted that gout and leukaemia can coexist. Talbott considers the association very rare, having met with it only once. Reifenstein (1939) observed a patient over a five-year period,

who presented himself with symptoms of polycythaemia and a blood uric acid of 5·3 mg. per 100 c.cm., and who subsequently developed gout and later myeloid leukaemia. Tinney and his co-workers (1945), as stated before, have made a very complete study of polycythaemia, and report that in 8 out of 168 patients the disease was associated with gout. They state that the coexistence renders mild gout severe, and severe gout difficult to control. In these combined cases the uric acid level was not proportionately higher. Lambie (1940) reports a case of chronic erythronoclastic anaemia in which gout developed. Acute attacks of gout have followed intense liver therapy and large doses of vitamin B_1 (Wright, 1945; Talbott, 1946; Herrick and Tyson, 1936; Krafka, 1935; Vorhaus and Kramer, 1938).

Diagnosis

Talbott (1940) considers that gout may be suspected, even before the first acute attack, when, acting on the evidence of a strong family history, the serum uric acid is found to be raised. The suspicion is strengthened if the patient passes a urinary calculus. After the development of an attack in the joints, additional evidence may be obtained from the therapeutic response to colchicine, the finding of a tophus, and signs of renal impairment. In the first years after the onset of an acute attack radiological examinations are usually negative apart from a hazy appearance from soft tissue swelling (Kamberg, 1943). Punched-out areas in the subchondral region represent foci of sodium urate deposition, and lead to a worm-eaten appearance. They usually appear late and are not pathognomonic, since they may occur also in rheumatoid arthritis. Talbott states that to diagnose gout from a punched-out area is as unreliable as to exclude it because the radiological findings are negative.

The Sedimentation rate.—The sedimentation rate of the red cells is not usually regarded as a particularly useful test in the diagnosis of gout. Wright (1945) states that it is usually increased during acute exacerbations. Haden and Kinell (1942) found that it was raised in 87 of 100 cases of gout, with an average level of 0·94. This compared with a level of 0·24 in 50 normal controls, 0·58 in 100 osteo-arthritic, and 0·98 in 100 rheumatoid arthritic patients. These authors state that the sedimentation rate quickly returns to normal after an acute attack, and is generally highest in the chronic progressive stage of gout. No relation was found between the sedimentation rate and the level of the blood uric acid. These findings accord with general experience, though the rate reported appears unexpectedly high. The writer has also noted a tendency for the blood sedimentation rate to return rapidly to normal as an acute attack subsides, and this fact may assist in the diagnosis of atypical cases. The application of the therapeutic test with full doses of colchicine is now universally advocated. The results may be spectacular, but only if full doses are given. Talbott (1946) warns that inadequate doses may mislead. Lockie (1939), agreeing with this, also thinks that the low-carbohydrate, low-protein, high-fat diet is a useful provocative test, and he quotes success in nine out of ten experiments. This is in direct contrast to the findings of Kersley and Gibson (1938) when they experimented unsuccessfully with ketogenic diets.

Prognosis

Most writers agree that, while the disease progresses in all patients after the first acute attack, the rate of progression is an unknown quantity. The more frequent and more severe the attacks, the more rapid the development of chronic permanent changes. It seems clear, too, that the younger the patient the greater the degree of crippling. Talbott has not seen a single case in which, if the first attack occurred over the age of fifty, serious polyarticular lesions developed. Expectation of life depends upon the degree of renal impairment. A patient may live for many years with advanced joint disease, but only a short time with severe kidney damage.

Treatment

Gout is incurable. If we accept a hereditary basis, then the problem of prevention is a eugenic one. Where there is a strong family history, possible precipitating factors (alcohol, dietetic indiscretions, sedentary life, etc.) should be avoided.

No new therapeutic discoveries emerge from a study of the literature. Colchicine in adequate doses is now universally used. Controversy rages round the toxicity of cinchophen, the relative values of low-fat or low-purine diets, the value of exercise or rest, and the effects of alcohol in its various forms. Talbott (1942) stresses the importance of an abundant fluid intake to combat dehydration (due to sweating and diuresis) and to allay precipitation of urate in the kidneys. Broths, fruit juices, and milk—fluids which contain minerals as well as calories—should be given. Most writers follow tradition in advocating strict reduction in purines. Bartels (1939) strongly recommends a low-purine, low-fat, high-carbohydrate diet both during and in between attacks, and so supports the earlier claims of Lockie and Hubbard (1934). Extra vitamins are added to make up for the deficiencies in A, D, and B_1. Bauer and Klemperer (1942) state on the other hand that omission of fat has not appeared to them beneficial, that high-fat diets have not precipitated attacks, and that the amount of fat contained in a well-balanced diet is insufficient to cause any significant retention of uric acid. Conclusive evidence is lacking, and opinions on this point vary widely.

There is little evidence in past or present literature to support the need for purine restriction. In a group of patients Talbott (1942) found that a measured low-purine diet had no effect on the frequency or severity of acute attacks. In the uncertain state of knowledge it seems reasonable to follow Talbott in advocating, according to tradition, a high-carbohydrate, soft diet for the acute attack, and a low-purine, normal-protein, moderate-fat, and high-carbohydrate diet in the intervening

periods. For the acute attack the value of colchicine is established, and it is generally agreed that dosage must be pushed to the point when it produces gastro-intestinal irritation. Buckley (1937) always prescribes it with ext. hyoscyamus to prevent griping. Its usefulness in the intervals between acute attacks, in doses varying from two $\frac{1}{120}$-grain tablets per week to two per day, is more controversial. It is strongly recommended by Talbott (1942) and Steinberg (1945), but Bauer and Klemperer (1942) deny any value for it as a preventive measure.

The use of urate diuretics between attacks continues to be advocated, and there are rival claims for cinchophen on the one hand and salicylates on the other. Most American workers dislike cinchophen and consider it dangerous. Jennings (1937) was among the first to establish by original work the value of salicylate, and among others Talbott, Bauer, and Klemperer consider that it is as effective as cinchophen. Many writers, including Kersley (1946) in this country, and Wright (1945) in Canada, consider that the risks of cinchophen, while admittedly real, have been overrated, and advocate its use when salicylate fails to produce the desired effect.

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THE HEBERDEN SOCIETY

ANNUAL GENERAL MEETING

The Heberden Society held the annual general meeting for the year 1946 at 11, Chandos Street, London, on Oct. 25 and 26 last.

Proceedings began on Friday afternoon, Oct. 25, with election of the following officers for the ensuing year: President, Mr. S. L. Higgs; Treasurers, Dr. C. B. Heald and Dr. E. Fletcher; Secretary, Dr. K. Stone (Junior secretary, appointment deferred); Ordinary Members of Committee, Drs. C. W. Buckley,* W. S. C. Copeman, G. D. Kersley, M. Ray, and R. E. Tunbridge.*

Pleuropneumonia-like Organisms and Arthritis

Dr. G. M. Findlay then opened a discussion on future trends of research in rheumatoid arthritis by reading the paper on arthritis in rats and mice due to pleuropneumonia-like organisms published in this issue of the *Annals*, p. 153. A full discussion of Dr. Findlay's paper followed.

Dr. C. H. Andrewes said that the rodent arthritis which Dr. Findlay had described certainly deserved further investigation, particularly as a model infection for chemotherapeutic studies. The disease was more like some forms of chronic arthritis in man than were other kinds of arthritis which could be readily produced in animals; further, it was susceptible to gold therapy. Dr. Andrewes rather doubted if it would prove worth while to investigate more gold compounds in this condition, but felt that there was an enormous field open for those looking for entirely new leads in the chemotherapy of arthritis. Recent reported activity of streptomycin in this rodent arthritis was encouraging. Dr. Andrewes said he had been vainly trying to obtain a strain of the pleuropneumonia-like organism concerned; a number of workers seemed to have lost their cultures during the war.

Dr. E. Klieneberger-Nobel showed a number of lantern slides demonstrating the difficulties of direct observation of pleuropneumonia-like organisms in the original material; and then the morphology of pure cultures in liquid and on solid media.

Dr. Henderson-Begg said that, working in collaboration with Dr. A. H. Harkness of St. Peter's Hospital, he had recently been culturing material from cases of non-specific urethritis and cervicitis, and cases of Reiter's disease, for pleuropneumonia-like organisms. The team had to date isolated organisms of this group from approximately twenty-five cases. Attempts to culture these organisms from the blood, synovial fluid, and conjunctival secretion of cases of Reiter's disease had been unsuccessful. The strains isolated from the urethral and cervical discharges of these non-specific cases comprised a homogeneous collection whose species specificity was suggested by their failure to infect laboratory animals. It would appear not unlikely that these organisms led a saprophytic existence in the female genital tract and that, under appropriate conditions, they might give rise to infection in the male. Whether they were responsible for the complicating arthritis and conjunctivitis of the so-called Reiter's disease remained to be seen.

Lt.-Col. R. R. Willcox said that, though he was diffident to enter the discussion, he did feel while listening to Dr. Findlay's paper that the profession might be on the threshold of something big. In the field of venereal disease there were certain conditions associated with rheumatism, such as Reiter's disease and keratosis blennorrhagica, which were laid at the door of the gonococcus with varying degrees of insistence. On occasion it was impossible to prove these as gonococcal in origin, and, indeed, sometimes all the available evidence indicated the opposite. It might well be that pleuropneumonia-like organisms, in symbiosis with, and occasionally without, the gonococcus, were responsible. Reiter's disease was not uncommon in the Army; its course was not influenced by penicillin, and hyperthermy was the best available treatment. Gold salts, however, did benefit, though the treatment by this means was more prolonged. Col. Willcox had recently treated two such cases with gold with satisfactory results. It was noted that, experimentally, the pleuropneumonia-like organisms did not respond to penicillin but did so to gold and streptomycin. Reiter's disease showed similar characteristics in regard to penicillin and gold, and it might well be, if streptomycin should prove effective, that the hypertherm would then be put out of business.

Dr. D. G. ff. Edward said he had no personal experience with pleuropneumonia-like organisms capable of causing arthritis, but he had been interested in the possibility that members of this group might be the cause of diseases, in man and animals, which were at present of unknown aetiology. A number of observations suggested that present methods might be very imperfect for isolating some members of the group. Recently, at the suggestion of veterinary colleagues, Dr. Edward had examined some cervical discharges from a herd of cows with a high incidence of infertility. Two cows yielded primary cultures of what he regarded as pleuropneumonia-like organisms, but growth could not be obtained on subculture. Sabin, also, in cultures

* Elected to fill vacancies occasioned by retirement of Drs. Pennington and Patterson.

from minced human tonsils found what he called "X" colonies, resembling pleuropneumonia-like colonies, but incapable of subculture. It was, therefore, possible that organisms of this group occurred which needed for their growth something not present in the media usually employed, but perhaps supplied in sufficient amount by the original inoculum to allow the primary culture only. Dr. Edward had found that the serum agar medium usually employed for growing this group of organisms gave variable results, depending on the batch of serum. Consistently good growth was obtained by adding yeast extract. The pleuropneumonia-like organisms responsible for infectious catarrh in mice failed to give surface colonies in plates in primary culture and needed a semi-solid or fluid medium for isolation. These were all technical points, but Dr. Edward said he mentioned them to suggest that, with our present lack of knowledge and imperfect means for isolating and investigating pleuropneumonia-like organisms, negative cultures did not exclude the possibility that a particular infection was due to a member of the group.

Dr. Mervyn Gordon described some experimental observations carried out with a virus that, when its virulence had developed to the highest degree by passage, was found to manifest a selective pathogenic action on fibrous tissue. This M4 virus of Tulloch, which appeared to be an exceptionally pathogenic strain of vaccinia (or variola), had been isolated by Sobernheim from smallpox crusts collected from the beds of cases at Dundee and pooled. For its isolation, Sobernheim used rabbits; and he employed the testicular route.

Dr. Mervyn Gordon said that the fibrositic capacity of M4 virus came to notice accidentally in the following manner. During 1938 a discussion on rheumatism was to take place in the autumn, so an attempt was made to see whether, by repeated injection intravenously, this M4 virus could produce endocarditis in rabbits in the same manner that certain bacteria do—notably streptococci. When M4 virus was tried in this way, however, no endocarditis was observed, but the rabbits developed periarthritis from inflammatory swelling and oedema of the fibrous tissue around the affected joint; especially that forming the supporting framework and sheathing of the muscles, tendons, and groups of blood vessels and nerves. In the local serofibrinous exudate, the M4 virus was present in pure culture and large quantity, and the cells were chiefly lymphocytes. It was only when the virulence of M4 was at its highest pitch that fibrositis was produced by it (*Annals of the Rheumatic Diseases*, Vol. 1, January, 1939; and *Lancet*, May 4, 1946). The interest of these observations lay in the resemblance between the lesions produced by M4 virus experimentally in rabbits and those present in man during rheumatism. In considering the history of our knowledge of rheumatism, Stockman pointed out that Scudamore, who published the first treatise in English on rheumatism in 1827, made a contribution of great value in that he recognized very definitely the true morbid anatomy of rheumatism—that the essential lesion is an inflammation affecting the white fibrous tissues of the body. Scudamore's definition of rheumatism was: "Pain of a peculiar kind, usually attended with inflammatory action affecting the white fibrous textures belonging to muscles and joints, such as tendons, aponeuroses, and ligaments; the synovial membranes of the bursae and tendons; and nerves". The nodes of Heberden and Aschoff appear to be incidents of this general fibrositis. But Stockman, who agreed that these experimental lesions were similar to those present in rheumatism, pointed out that fibrositis can be produced by other factors than the M4 virus. Among these Scudamore, in 1827, instanced variable temperature, direct cold, and moisture.

Dr. Gordon said it might be added that, in an article on acute rheumatism of children, in Vol. 3 of Allbutt's *System of Medicine*, first edition, 1897, Cheadle figured two sections to illustrate the changes produced—one of a subcutaneous node, the other of a mitral valve. Both showed the same lesion, namely acute fibrositis. Aschoff's nodes were not described until 1904, but from a study of the beautiful illustrations to his article in these *Annals*, Vol. 2, July, 1939, and from direct observation, there was little doubt that they originated in the fibrous tissue of the heart as well. Thus in acute rheumatism the main changes in the heart were brought about by a cardiac fibrositis the main effect of which was most evident on its coverings. Ultimately, in prolonged cases of subacute rheumatism, the fibrous tissue might undergo amyloid degeneration.

Erysipelothrix Polyarthritis of Swine

Dr. D. H. Collins then spoke on erysipelothrix polyarthritis of swine. He described observations on a series of field cases of sporadic arthritis in pigs in which the causative organism frequently proved to be *Erysipelothrix rhusiopathiae*, and in which the lesions were found to be a non-suppurative proliferative arthritis of the larger joints of all four limbs. Experimental induction of a similar type of polyarthritis followed the repeated intravenous inoculation of broth cultures of either of two strains of the micro-organism. The arthritis had also been proved to be contagious, young, healthy pigs developing signs of the disease after only a few days of contact with field cases. The disease of the joints was clearly of bacteraemic origin, and its pathological characteristics included synovial proliferation, pannus formation with superficial erosion of articular cartilage, diffuse and focal lymphoid infiltrations in the synovial villi, and progression of the arthritis even after apparent sterilization of the joint cavities and tissues. Other organs were also occasionally involved. Verrucose endocarditis, pericarditis, focal necrosis of myocardium and of liver, and peripheral arteritis were seen in some animals. Most of this work had been undertaken before the war with Dr. W. Goldie at Leeds, and had been published (*J. Path. Bact.*, 1940, **50**, 323). Dr.

Collins stated that erysipelothrix did not seem to cause arthritis in man. He pointed out certain similarities, on the one hand with the arthritis of rodents caused by pleuropneumonia-like organisms just described by Dr. Findlay, and on the other hand with the rheumatoid type of human arthritis, which he thought, by analogy, must surely be of infective origin.

A short film illustrated the disabilities and signs manifest in the affected animals, and a number of lantern plates showed the gross and microscopical pathological changes.

Annual Dinner

The Annual Dinner of the Society was held at the Junior Carlton Club on Friday, Oct. 25. The dinner, marking the tenth anniversary of the Heberden Society and of the Empire Rheumatism Council, was attended by the President of the Royal College of Physicians, Lord Moran, and many distinguished guests, including Lord Horder, Dr. Mervyn Gordon, General Sir Alexander Biggam, Dr. C. H. Andrewes, Dr. Loring Swaim, Dr. G. M. Findlay, and Professor Axel Höjer, Chief Medical Officer to the Swedish Ministry of Health.

After dinner the President, Dr. Buckley, proposed the toast of "The Campaign against Rheumatism". He said that we were at the beginning of a new phase, of which the first objective was to educate the general practitioner in the recognition of early manifestations of the rheumatic diseases. Professor Davidson, in replying, said that hitherto scientific and clinical work in this group of diseases might have been below the standard required to secure support from the authorities: but he had every confidence in future work to elucidate these problems.

Rheumatism in Sweden

On Saturday morning the meeting was concluded with an address by Professor J. Axel Höjer, Chief Medical Officer, Royal Swedish Ministry of Health. This meeting was held in association with the Empire Rheumatism Council, Lord Horder took the Chair, and the Guest of Honour was His Excellency the Swedish Minister, M. B. G. Frytz. It is hoped to publish Dr. Höjer's address on the organization and work of a rheumatic service in Sweden in the next issue of these *Annals*.

A vote of thanks to Professor Höjer was proposed by Sir Wilson Jameson, who said that the Ministry of Health in this country would derive great help from the experience and plans in Sweden. He felt that our Ministry could make a big contribution to further progress.

FELLOWSHIP OF POSTGRADUATE MEDICINE

WEEK-END COURSE IN CHRONIC RHEUMATISM

The Fellowship of Postgraduate Medicine, in association with the University of Bristol, held a successful week-end course in chronic rheumatism at the Royal National Hospital for Rheumatic Diseases, Bath, from Friday, Aug. 23 to Sunday Aug. 25, 1946, inclusive.

On Friday, after a visit to the Spa baths, Dr. P. W. McKeag delivered a clinical lecture on osteo-arthritis. Saturday morning began with a clinical lecture and demonstration on rheumatoid arthritis by Dr. G. D. Kersley. Mr. Charles Kindersley then demonstrated orthopaedic treatment plaster technique, and physical methods of treatment. In the afternoon there were clinical lectures on fibrositis by Dr. J. B. Bennett, on *x*-ray diagnosis and treatment by Dr. G. D. Steven, and on sciatica by Dr. Lovell Hoffman. On Sunday morning Dr. L. C. Hill delivered a clinical lecture on gout, which was followed by a lecture and demonstration on pathological principles by Dr. Hubert Gibson, and by a clinical lecture on spondylitis by Dr. G. D. Kersley. In the afternoon Dr. L. C. Hill lectured on arthritis due to specific organisms, and Dr. M. H. L. Desmarais on rehabilitation and convalescence in relation to industry and the duties of the welfare officer.

OBITUARIES

It is with regret that we record the deaths of two well-known workers in the field of rheumatic disease. Dr. G. R. P. Aldred-Brown, who died on July 26, was a recruit to medicine from the Army, in which he served as a captain in the R.F.A. in France from 1916 to 1918. On leaving the Army, he studied medicine at the London Hospital, qualifying M.B., B.Ch. in 1924. In 1938 he became a Doctor of Medicine. He was for a time pathologist and bacteriologist to the Dorset County Hospital, but later removed to Bath, and in 1930 joined the staff of the Royal Hospital for Rheumatic Diseases, where he was senior physician until shortly before his early death. While at Bath he made the Rheumatic Hospital his main interest, becoming a Governor in 1932. During the war years, until ill health caused him to reduce his output of work, it was largely his influence which kept alive a spirit of keenness and desire for progress within the hospital. Though at the time of his death he had just retired from the active staff and had been appointed a Consulting Physician, he will be sorely missed by both patients and staff. Among his more important contributions to medical literature may be mentioned *Blood Sedimentation Rate and Plasma Proteins* (*Lancet*, 1934), and *Plasma Proteins and Non-protein Nitrogen and Sedimentation Rate in Chronic Rheumatic Disorders* (*Quart. J. Med.*, 1935), both of which are valuable studies in a subject the importance of which is becoming more generally recognized. His early death is a loss both to the campaign against rheumatism and to the city of his adoption.

Professor Bogomoletz died at Kiev, where he was President of the Ukrainean Academy of Sciences. He was best known in Great Britain on account of the serum which he discovered and which he named anti-reticular cytotoxic serum. It was claimed to have striking effects in rheumatism as well as in other diseases. Investigations in this country, however, failed to substantiate the claims that were made. Had it not been for his death, further observations might have been carried out in the light of more information about the technique he used.

Dr. Bertram Nissé, Physician to the Red Cross Clinic for Rheumatic Diseases, died in London on August 14. Bertram Sydney Nissé was educated at St. Olave's School, London, and with a Buxton Arts Scholarship entered the London Hospital, where, in 1921, he qualified M.R.C.S., L.R.C.P. He obtained the M.B., B.S. a year later, and the M.R.C.P. in 1925. In 1924 he had been awarded the University Gold Medal for his M.D. thesis. After holding house appointments and a pathological assistant-ship at the London Hospital, he became resident medical officer at the National Hospital for Diseases of the Heart, and later was appointed chief assistant at the National Heart Hospital. Becoming convinced that it was important to raise the standard of teaching and research into the rheumatic diseases, he and a number of colleagues founded the British Red Cross Clinic in 1930. Throughout the 1939–45 war, Dr. Nissé deputized for Dr. W. S. C. Copeman, who was on war service, as physician in charge of the rheumatism clinic at the West London Hospital. He was a member of the International Society for Medical Hydrology and a vice-president of the Physical Medicine section of the Royal Society of Medicine. His monograph on rheumatism, published in 1938, is a model of compactness and lucidity, and readers will also recall articles from his pen which appeared in the *International Journal of Medicine and Surgery* (1930) and in the *Clinical Journal* (1935). He was a kind and wise physician who did much toward furthering the clinical and scientific investigation of the rheumatic diseases, and he was one of those who has helped to make the nation more aware of the urgent problems these diseases create; his loss from among the ranks of rheumatologists will be deeply felt by colleagues and patients alike. Dr. Nissé married, in 1932, Miss Helena Jacobs of Newcastle, and to his widow, son and daughter we extend our sincere sympathy.